DEVELOPMENT AND EVALUATION OF MUCOADHESIVE PROPERTIES - IN VITRO AND EX VIVO STUDIES.

A Dissertation submitted to

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

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In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

REG. NO: 26105410

Under the guidance of

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SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

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This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

Signature of the Guide

K.MOHAN KUMAR., M.Pharm

DEDICATED TO

MY

FATHER

&

MOTHER

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Introduction

1. INTRODUCTION

Mucoadhesive controlled drug delivery systems are very beneficial, since they provide a controlled drug release over long period of time and localize the drug to a specific site of the body. The prolonged residence time of the drug in the body is believed to prolong duration of action. Mucoadhesive drug delivery system can be applied to any mucosal tissue in the body. Including the gastrointestinal, ocular, respiratory, buccal, nasal, rectal, urethral and vaginal path.[1]

Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element to design of these drug delivery systems. Mucus is composed of 95% water and about 5% mucus glycoproteins termed mucin, plus a large number of minor components.[2]

Mucoadhesion is provided by the formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers. Mediated by mucoadhesive polymers, the residence time of dosage forms on the mucosa should be prolonged, which allows a controlled drug release at a given target site to maximize the therapeutic effect.[3] Several classes of polymers have been proposed as mucoadhesive due to their ability to interact physically and/or chemically with the mucus, such as hydrogen bonds, Van-Der Waal forces, ionic interactions and/or chain entanglements, which are the most common.[2]

Increasing the retention time (mucoadhesion time) of the dosage form is therefore essential in the development of these systems and it has been shown to increase with an increase in the mucoadhesivity of the system. Maximizing the mucoadhesivity of these systems therefore remains an important goal in the development of mucoadhesive drug delivery systems. In addition to mucoadhesivity, a controlled release of the drug from the dosage form is also desirable. The potential advantages of this concept include the minimisation of drug related side effects and improved patient compliance. [4]

The oral cavity and oral mucosa is being increasingly used for the administration of drugs, which are the oral disintegration and buccal/sublingual route of medicaments into the systemic circulation.[5] Rapid orally disintegrating tablets may be used to achieve a fast onset of action. Alternatively, the buccal/sublingual route is also suitable for

medications that cannot or shall not be taken by the oral route due to instability of the drug at the low pH of the stomach, or their susceptibility to the hepatic first pass effect.[6]

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. The buccal mucosa, along with other mucosal tissues, has been investigated as a potential site for controlled delivery because of its accessibility and low enzymatic activity compared to the gastro-intestinal tract. Another interesting advantage is its tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers. [7]

Mucoadhesive polymers are used to immobilize a drug delivery device on a specific site for targeted release and optimal drug delivery due to intimacy and duration of contact. Mucoadhesive polymers have been developed for buccal, nasal, ocular, vaginal and oral applications. So far, a considerable number of studies focusing on the mucoadhesive properties of wide range of polymeric materials, particularly hydrophilic polymers containing numerous hydrogen bond (H-bond) forming groups, have been performed. It has been proposed that the interaction between the mucus and mucoadhesive polymers is a result of physical entanglement and secondary bonding, mainly H-bonding and van der Waals attraction. These forces are related to the chemical structure of the polymers. The types of surface chemical groups of mucoadhesive polymers that contribute to mucoadhesion include hydroxyl, carboxyl, amine and amide groups in the structure.

There are many factors affecting the mucoadhesive properties of polymers, such as degree of hydration, ionic strength of medium & their molecular feature. The strategy for designing buccoadhesive is based principally on the utilization of polymers with suitable physicochemical properties.[5] The use of acrylic-based polymers can be very beneficial to overcome the shortcomings of oral drug administration. Acrylic-based polymers have been extensively used for mucoadhesive applications, since they exhibit very high adhesive bond strength in contact with tissues. Thus, they allow the localization of the drug at the site of absorption.[1]

Additionally, mucoadhesive properties of polyacrylic acid cross linked polymer depending on the physical properties. Example: solution, gel forming & swelling properties of carbopol are different due to types or characteristics of carbopol.[5]

HPMC is well known as one of the most effective mucoadhesive polymers. HPMC is a

hardly water-soluble polymer carrier with the ability to swell on contact with aqueous solutions, creating a hydrocolloid gel mass on the external surface. This mass gradually dissolves during time. Therefore, from such a system, the release of the active ingredient is expected to be controlled by the dissolution rate of the polymer gel in mucus.[8]

Studying the performance of mucoadhesive polymers has become an increasingly important tool for designing mucoadhesive drug delivery system. The current study intends to assess the adhesive properties of different polymer ratios by using goat buccal mucosa.[9]

Direct compressed tablets prepared from mucoadhesive polymers can be effectively utilized as vehicles for the delivery of various therapeutic molecules. In the present study includes development and evaluation of mucoadhesive hydrophilic compressed tablets for buccal delivery by using atorvastatin calcium as model drug.

Atorvastatin calcium, which is an antihyperlipidemic drug with low water solubility and high membrane permeability included in BCS II. The formulations were prepared by direct compression method and investigated for physicochemical adhesive and release characteristics.

Review of Literature

2. REVIEW OF LITERATURE

2.1 REVIEW OF MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye.[10]

2.1.1 MECHANISM OF MUCOADHESION

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The most research has described bioadhesive bond formation as a three step process:-

STEP1: Wetting and swelling of polymer

STEP2: Interpenetration between the polymer chains and the mucosal membrane.

STEP3: Formation of Chemical bonds between the entangled chains.[11]

Fig 1: The Two Steps of Mucoadhesive Process

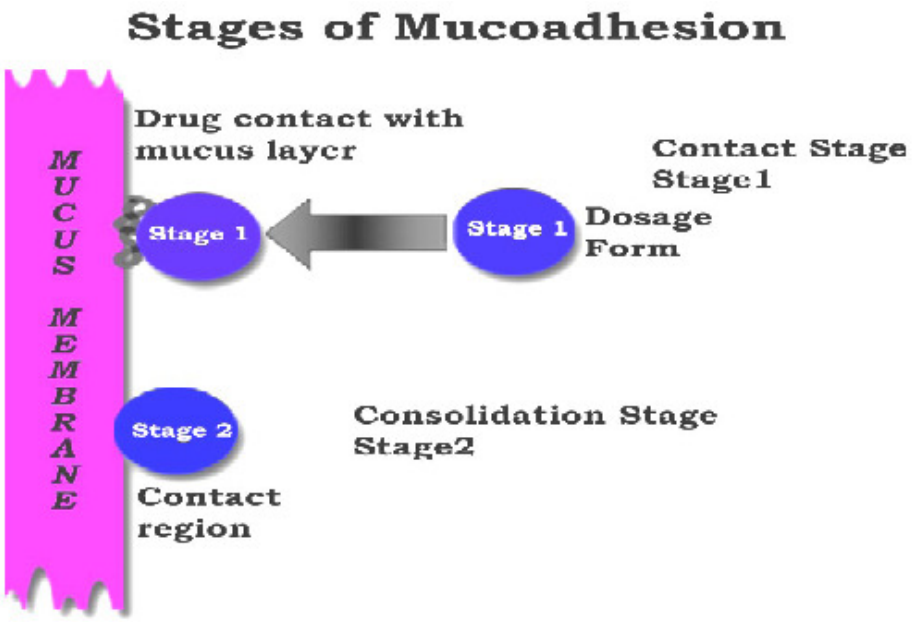
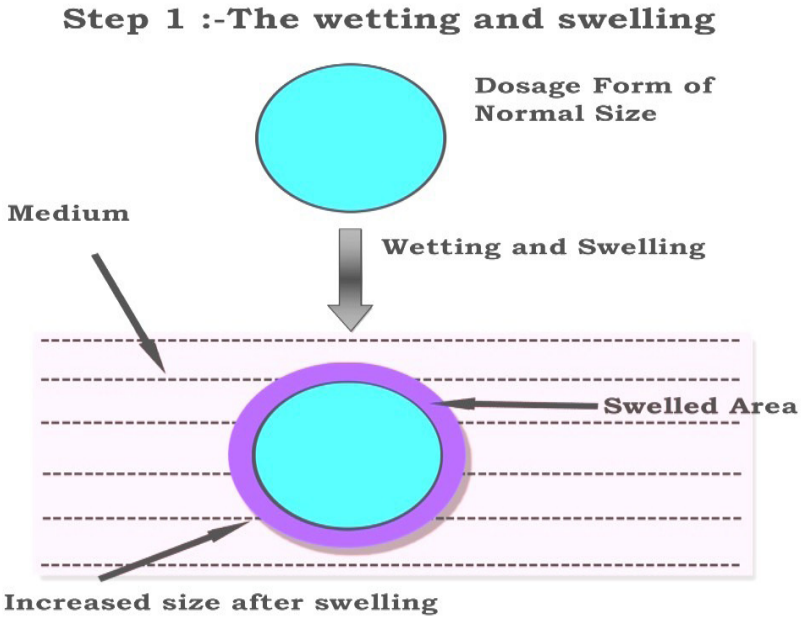


Fig 2: Wetting and Swelling of Polymer



2.1.2 ADVANTAGES OF BUCCAL DRUG DELIVERY

- Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism.
- Improved patient compliance due to the elimination of associated pain with injections.
- A relatively rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued.
- Increased ease of drug administration
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Extent of perfusion is more therefore quick and effective absorption.
- Nausea and vomiting are greatly avoided.
- Used in case of unconscious and less co-operative patients.
- Drugs, which show poor bioavailability via the oral route, can be administered conveniently.

  ***Example*:** Drugs, which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine**.**

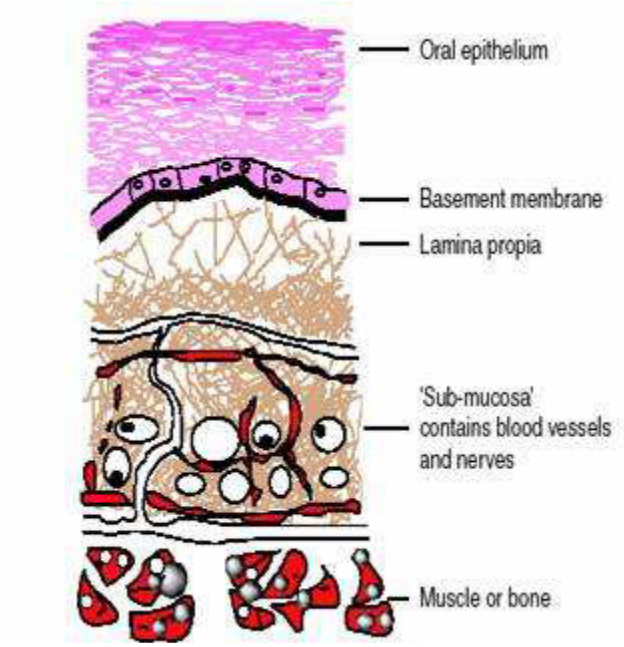
2.1.3 LIMITATIONS OF BUCCAL DRUG DELIVERY

- Drugs which irritate oral mucosa or have bitter taste, or cause allergic reactions, discoloration of teeth cannot be formulated.
- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- The patient cannot eat/drink.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug Low permeability of the buccal membrane, specifically when compared to the sublingual membrane.[11]

2.2 OVERVIEW OF BUCCAL MUCOSA[11]

A. Structure

FIG 3: CROSS SECTION OF ORAL MUCOSA



The oral mucosa is anatomically divided into

- Epithelium
- Basement membrane and Connective tissues

Epithelium: The epithelium consists of approximately 40–50 layers of stratified squamous epithelial cells having thickness 500-800µm. The epithelium of the oral mucosa serves as a protective covering for the tissues and a barrier to the entry of foreign materials. The uppermost layers form a surface that is resistant to physical insult and to penetration by foreign substances.

Basement Membrane and Connective Tissue: The basement membrane (BM) is a continuous layer of extracellular materials and forms a boundary between the basal layer of epithelium and the connective tissues. This basal complex anchors the epithelium to the connective tissue and supplements the barrier function of the superficial layers of the epithelium to prevent some large molecules from passing the oral mucosa.

B. Environment

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva.

Role of Saliva

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel.
- To hydrate oral mucosal dosage forms.

Role of Mucus

- Made up of proteins and carbohydrates.
- Cell-cell adhesion.
- Lubrication.
- Bioadhesion of mucoadhesive drug delivery System.

2.3 TYPES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS[12]

1. Gastrointestinal bioadhesive drug delivery systems.
2. Buccal bioadhesive drug delivery systems
   i. Adhesive tablets
   ii. Adhesive gels
   iii. Adhesive patches
3. Sublingual bioadhesive drug delivery systems
4. Ocular mucoadhesive drug delivery systems
5. Nasal bioadhesive drug delivery systems
6. Rectal bioadhesive drug delivery systems
7. Vaginal bioadhesive drug delivery system

2.4 FACTORS INFLUENCING DRUG ABSORPTION FROM THE ORAL CAVITY

As the oral mucosa is a highly vascular tissue, the main factors that influence drug absorption from the mouth are:

a) The permeability of the oral mucosa to the drug.
b) Physicochemical characteristics of the drug.

c) Miscellaneous factors.

d) Polymer-related factors.[12]

2.5 EVALUATION OF BUCCAL TABLETS[13]

- ♠ In vitro swelling rate and bioadhesion studies
- ♠ In vitro surface pH studies
- ♠ In vitro drug release studies
- ♠ In vitro permeation studies
- ♠ In vitro mucoadhesion strength
- ♠ In vitro residence time
- ♠ In vivo release studies
- ♠ Stability studies in human saliva
- ♠ Ex vivo mucoadhesion time
- ♠ Ex vivo mucoadhesion force
- ♠ Ex vivo transmucosal permeation studies

2.6 EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES[14]

Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

A. In vitro permeation method

At the present time, most of the *in vitro* studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers (usually Krebs buffer) until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments. Buccal cell cultures

have also been suggested as useful in vitro models for buccal drug permeation and metabolism. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled.

B. In vivo Methods

In this method the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber (to determine the amount of drug remaining in the chamber) and blood samples are drawn after 0 and 30 minutes (to determine amount of drug absorbed across the mucosa).

2.7 MUCOADHESIVE POLYMERS[10]:

Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.

1. The polymer and its degradation products should be nontoxic and non absorbable in the gastrointestinal tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong non covalent bond with the mucin epithelial cell surface.
4. It should adhere quickly to moist tissue and should possess some site specificity.

5. It should allow easy incorporation of the drug and offer non hindrance to its release.
6. The polymer must not decompose on storage or during shelf-life of the dosage form.
7. The cost of polymer should not be high.

Some of the mucoadhesive polymers along with their mucoadhesive property are summarized below:

Table 1: Mucoadhesive polymers with their mucoadhesive property

1	Carbopol 934	**+++**
2	Carboxy methyl cellulose	**+++**
3	Polycarbophil	**+++**
4	Tragacanth	**+++**
5	Sodium alginate	**+++**
6	Hydroxy ethyl cellulose	**+++**
7	Hydroxy propyl methyl cellulose	**+++**
8	Gum karaya	**++**
9	Guar gum	**++**
10	Poly vinyl pyrrolidone	**+**
11	Polyethylene glycol	**+**

Note: +++ excellent, ++ fair, +poor

2.8 INNOVATIVE DRUG DELIVERY SYSTEMS

Innovative drug delivery systems, such as lipophylic gel, buccal spray and phospholipid vesicles have been recently proposed to deliver peptides via the buccal route. In particular, some authors proposed the use of cubic and lamellar liquid crystalline phases of glyceryl monooleate as buccal drug carrier for peptide drugs. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been recently developed, and it is now in clinical phase II trials. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. Levels of drug in the mouth are dramatically increased compared with conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal

epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.

Phospholipid deformable vesicles, transfersomes, have been recently devised for the delivery of insulin in the buccal cavity. They are morphologically similar to liposomes, but have the peculiarity of responding to external stresses by rapid shape transformations requiring low energy. This high deformability allows them to deliver drugs across epithelial barriers. To prepare these vesicles, surfactants, such as sodium cholate or sodium dehoxy cholate are incorporated into the vesicular membrane. The insulin administration in rabbits surpasses that seen with traditional liposomes: compared with subcutaneous administration of insulin solution, the bioavailability of deformable vesicles was significantly greater than that of the conventional vesicles. It is necessary to underline that several formulations described here have been tested in animal models that possess buccal mucosa different to that of human. For such formulations, more significant information could be derived from tests performed on other animal models that better simulate humans or in human volunteers.[15]

REVIEW OF RELEVANT WORKS

G. Ikinci et al. developed a bioadhesive buccal tablet for the delivery of nicotine into the oral cavity. Carbomer and alginic acid sodium salt were used as bioadhesive polymers in combination with hydroxy propyl methylcellulose at different ratios. In vitro release and bioadhesion studies were performed on the developed tablets. In the formulations containing CP: HPMC, the NHT release increased with the increasing HPMC concentration whereas a decrease was observed with increasing HPMC concentration in formulations containing NaAlg: HPMC. The bioadhesive properties of the tablets containing NaAlg:HPMC was not affected by the concentration of the NaAlg but increased significantly with the increasing CP concentration. The developed

formulations released NHT for 8 h period, and remained intact except for the formulation containing CP: HPMC at 20:80 ratio.[16]

S. S enel et al. designed a bioadhesive tablet formulation for buccal delivery using a mixture of hydroxypropyl methylcellulose and carbomer, incorporated with a penetration enhancer, sodium glycodeoxycholate (GDC). In vitro bioadhesion property of the formulated tablet was examined and histological study was carried out to examine an in vivo interaction between the tablet and tissue. GDC did not affect the adhesiveness of the tablet which makes it an acceptable excipient for a buccal bioadhesive drug delivery system. Histological changes such as loss of upper cell layers and formation of vacuoles as well swelling in the cells were observed in the buccal epithelium, after 4 h contact with the tablets containing GDC.[17]

Mahalaxmi D. et al. formulated and evaluated buccal tablets of glipizide, an antidiabetic drug. Tablets of glipizide were prepared by direct compression method using bioadhesive polymers like Carbopol 974P, Methocel K4M and Methocel K15M in different concentrations. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, *ex vivo* bioadhesive strength, *in vitro* drug release, *ex vivo* drug permeation and FTIR studies. The tablets were evaluated for *in vitro* release in pH 6.8 phosphate buffer for 8 hr in standard dissolution apparatus. The optimized formula followed non-fickian release mechanism with zero order kinetics. MethocelK15M in the ratio of 1:2 could be used to design effective and stable buccoadhesive tablets of glipizide.[18]

C.F. Wong et al. carried out a study for measuring the bioadhesive properties of polymers under simulated buccal conditions by a method using a texture analyzer equipment and chicken pouch as the biological tissue. The method was evaluated using two polymers, namely Carbopol 974P and Methocel K4M. The parameters measured were the work of adhesion and peak detachment force. When the method was applied to determine the bioadhesiveness of several polymers, the values obtained for the work of adhesion and peak detachment force were quite consistent in the ranking of the polymers. The Carbopol were found to have the highest values, followed by gelatin, sodium

carboxymethyl celluloses and hydroxypropylmethyl celluloses. On the other hand, Alginic acid, Eudragit RLPO and RSPO, and Chitosan appeared to have low bioadhesive values.[19]

L. Perioli et al. prepared mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives in order to obtain new formulations containing metronidazole for periodontal disease treatment. All the prepared tablets were characterized by swelling studies, ex vivo and in vivo mucoadhesive time, ex vivo mucoadhesion force, in vitro and in vivo release. The best mucoadhesive performance and the best in vitro drug release profile were achieved by using hydroxyethyl cellulose and carbomer 940 2:2 ratio. The chosen tablet, containing 20 mg of metronidazole, performed 12 h drug sustained release with buccal concentrations always higher than its Minimum Inhibitory Concentration.[20]

N.A. Nafee et al. prepared and evaluated mucoadhesive patches containing 10 mg miconazole nitrate. The patches were prepared with ionic polymers, sodium carboxymethyl cellulose (SCMC) and chitosan, or non-ionic polymers, polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and hydroxypropylmethyl cellulose. Patches exhibited sustained release over more than 5 h and the addition of polyvinyl pyrrolidone (PVP) generally enhanced the release rate. Optimum release behavior was shown with patches containing 10% w/v PVA and 5% w/v PVP. In vivo release study concluded that this formulation has uniform and effective salivary levels with adequate comfort and compliance during at least 6 hours.[21]

C. Remunan-Lopez et al. carried out a study describing the preparation of new buccal bilayered devices comprising a drug-containing mucoadhesive layer and a drug-free backing layer, by two different methods. Bilaminated films were produced by a casting / solvent evaporation technique and bilayered tablets were obtained by direct compression. The mucoadhesive layer was composed of a mixture of drug and chitosan, with or without an anionic crosslinking polymer (polycarbophil, sodium alginate, gellan gum), and the backing layer was made of ethylcellulose. Using nifedipine and

propranolol hydrochloride as slightly and highly water-soluble model drugs, respectively, it was demonstrated that these new devices show promising potential for use in controlled delivery of drugs to the oral cavity. The uncrosslinked chitosan-containing devices absorbed a large quantity of water, gelled and then eroded, allowing drug release. The bilaminated films showed a sustained drug release in a phosphate buffer of pH 6.4.[22]

S. Mohammadi-Samani et al. determined the effect of mucoadhesive polymers such as hydroxyl propyl methyl cellulose with viscosity grade 60 and 500 mPas, sodium carboxy methyl cellulose and carbopol 934 alone or in combination with each other on the release profile of prednisolone and evaluated the mucoadhesion strength of these buccoadhesive formulations. The results showed that the release of prednisolone from HPMC with viscosity grade 60 mPas and Cp 934 alone was fast and their mucoadhesion strengths was low. On the other hand, the release rates of prednisolone from the HPMC viscosity grade 500 mPas and NaCMC and mucoadhesion strengths were moderate and suitable. The results showed that with different blends of HPMC viscosity grade 500 mPas or NaCMC and Cp 934 with increasing in HPMC or NaCMC/Cp 934 ratio a remarkable decrease in the rate of drug release and an appreciable increase in the mucoadhesion strength was observed.[23]

H.G. Choi et al. studied the release and bioavailability of omeprazole delivered by buccal adhesive tablets composed of sodium alginate, hydroxypropylmethylcellulose, magnesium oxide and croscarmellose sodium for the development of omeprazole buccal adhesive tablets. The analysis of the release mechanism showed that croscarmellose sodium changed the release profile of omeprazole from first- to zero-order release kinetics by forming porous channels in the tablet matrix. The tablet is composed of omeprazole–sodium alginate–HPMC–magnesium oxide–croscarmellose sodium (20:24:6:50:10 mg). It may be attached to the human cheek without collapse and it enhanced the stability of omeprazole in human saliva for at least 4 h, giving a fast release of omeprazole. The buccal bioavailability of omeprazole in hamsters was 13.763.2%. Thus the in vivo results demonstrated that the omeprazole buccal adhesive tablet would be useful to deliver omeprazole which degrades very rapidly in acidic aqueous medium and undergoes hepatic first-pass metabolism after oral administration.[24]

E. Karavas et al. prepared a pulsatile release formulation consisting of two-layered tablets. The active core was constituted by a FELO/PVP 10/90 w/w solid dispersion while for the adjustment of the drug release time the coating layer was composed of PVP/HPMC blends at different compositions, acting as a stimulus responsible layer. The miscibility of the system enhances the mucoadhesive properties of the blends, compared with those of pure HPMC, which is desired for such applications. The enhancement was attributed to the higher rate of wetting and flexibility of the new matrices due to the faster dissolution of the PVP macromolecules. Upon exposure of the prepared tablets to the release medium it was found that the coating layer disintegrates first, followed by the immediate release of FELO from the active core.[25]

A.P. Munasur et al. carried out the statistical optimization of mucoadhesivity and characterization of multi polymeric propranolol matrices for buccal therapy. A formulation of 20% PAA, 20% CMC and 20% PVP was identified for maximizing the mucoadhesivity. Reproducibility of the optimal formulation in terms of mucoadhesivity and controlled drug release was confirmed. The optimal formulation was characterized in terms of mucoadhesivity, release kinetics, swelling/erosion, hydration dynamics and surface pH. From the model fitting analyses, drug release was found to be diffusion, polymeric relaxation and erosion based with the former two being more dominant over erosion. Textural profiling showed initial rapid hydration, which could be beneficial for enhanced mucoadhesivity. Surface pH of the multipolymeric matrices was similar to salivary pH and did not show extremes in changes over the test period. The optimal preparation of multipolymeric propranolol matrices identified in this study shows potential for buccal administration.[26]

Aim and Objective

3. AIM AND OBJECTIVE

Atorvastatin calcium is a antihyperlipidemic drug comes under the BCS Class II (low solubility and high permeability). It is known to have low oral bioavailability (14%) due to extensive high first-pass effect and its availability in less dose. In order to maintain the therapeutic concentration of atorvastatin calcium, modified release formulation are necessary.

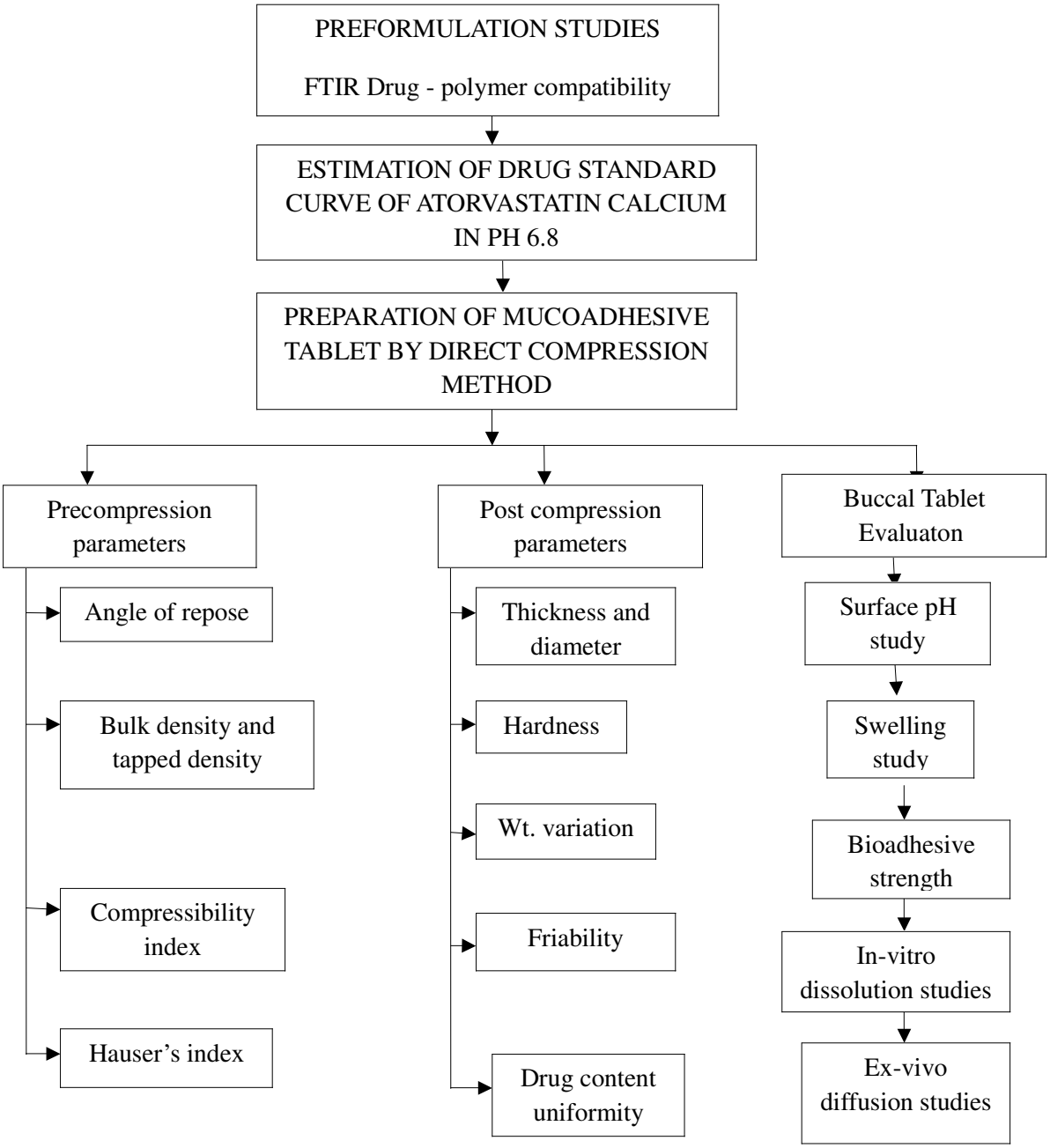
In the present work the mucoadhesive buccal tablets of atorvastatin calcium was prepared to prolong the residence time at the site of application (or) absorption, and to facilitate the intimate contact with the underlying absorption surface to improve and enhance the mucoadhesive properties.

The mucoadhesive buccal tablets of atorvastatin calcium were prepared by using Carbopol-934, Hydroxy propyl methyl cellulose K100M, Hydroxy ethyl cellulose and Polyvinylpyrolidone along with ethyl cellulose as an impermeable backing layer.

The most important goals in development and evaluation of mucoadhesion study consist of drug targeting at specific site of absorption, controlled releasing, increasing of residence time, decreasing the first pass effect and long term drug delivery.

Plan of Work

4. PLAN OF WORK



Profile

5. PROFILES

5.1 DRUG PROFILE

ATORVASTATIN CALCIUM [27,28]

Synonyms : Atorvastatina calcica,

Atorvastatine calcique,

Atorvastatinum calcicum; Calcii,

Atorvastatinum; CI-98.

Category : Antihyperlipidemic agent

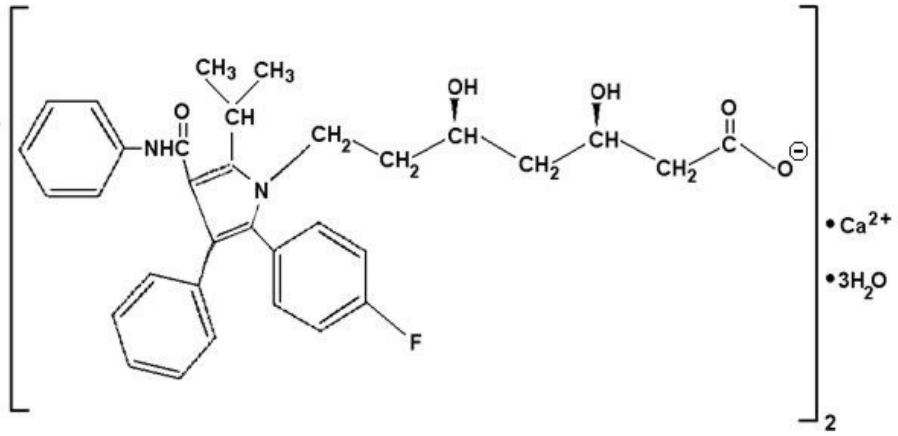
Empirical formula : $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$

Molecular weight : 1209.4

Chemical Name : Calcium -2-(p-fluorophenyl)-beta, delta-dihydroxy-5-isopropyl-3-phenyl-4-

(Phenylcarbamoyl) pyrrole-1-heptanoic acid (1:2) trihydrate**.**

Structure formula :



Functional Category : HMG-CoA reductase inhibitors .

Physicochemical properties

BCS classification : Class II (low solubility and high permeability).

Description

Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Clinical Pharmacology

Atorvastatin calcium is used along with diet, exercise, and weight-loss to reduce the risk of heart attack and stroke and to decrease the chance that heart surgery will be needed in people who have heart disease or who are at risk of developing heart disease. Atorvastatin is also used to decrease the amount of cholesterol (a fat-like substance) and other fatty substances in the blood. This will decrease the risk of stroke, heart attack, and other heart diseases because when there are high levels of cholesterol and other fats in the blood, these substances may build up along the walls of the blood vessels and decrease or block blood flow to the heart. Atorvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body.

Pharmacokinetics

Absorption

Rapidly absorbed; T_{max} is 1 to 2 h. Bioavailability is approximately 14%; low bioavailability is because of presystemic circulation in GI mucosa and/or hepatic first-pass metabolism. Food decreases rate and extent of absorption approximately 25% and 9%, respectively, but does not alter efficacy.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Metabolism

Undergoes hepatic and extra hepatic metabolism, including first-pass metabolism. Extensively metabolized to active metabolites, which produce approximately 70% of circulating inhibitory activity of HMG-Co A reductase.

Elimination

Atorvastatin and metabolites eliminated primarily in bile. Less than 2% of dose is recovered in the urine. Plasma $t_{½}$ is approximately 14 hours.

Duration

The $t_{½}$ of HMG-CoA reductase inhibition is 20 to 30 hours.

Contraindications

Active liver disease or unexplained persistent elevation of serum transaminases; pregnancy; lact.

Dosage and Administration

Adults

10 to 80 mg/day.

Heterozygous Familial Hypercholesterolemia Children 10 to 17 yr of age

Start with 10 mg/day (max, 20 mg/day).

Pharmacodynamics

Adverse Reactions

CNS **:** Headache, Asthenia, dizziness, insomnia.

ENT **:** Sinusitis, Pharyngitis, Rhinitis.

Dermatologic **:** Rash, Stevens-Johnson syndrome,
bullous rashes including erythema multiforme
Toxic epidermal necrolysis.

GI **:** Sinusitis, abdominal pain, constipation, dyspepsia, Nausea.

Genitourinary **:** Albuminuria, Hematuria.

Metabolic **:** Peripheral edema (at least 2%).

Musculoskeletal : Myalgia, Arthralgia, Arthritis, Rhabdomyolysis.

Respiratory **:** Bronchitis.

Miscellaneous **:** Accidental injury, flu-like symptoms, chest pain, Angioneurotic edema.

Drug Interactions

Co Administration of Antacids, cholesterol, rifampin may decrease atorvastatin levels. Azole antifungal agents (eg, itraconazole), cyclosporine, diltiazem, gemfibrozil, grapefruit juice, macrolide antibiotics (eg, erythromycin), niacin, NNRTIs, protease inhibitors (eg, ritonavir), verapamil, severe myopathy or rhabdomyolysis may occur.

5.2 POLYMER PROFILE

5.2.1 CARBOPOL 934P[29]

Nonproprietary names **:** BP: Carbomer

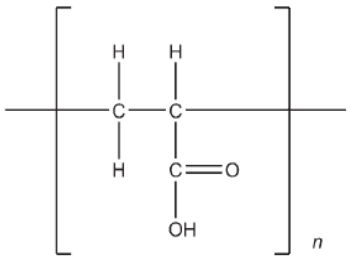
USP: Carbomer

Synonym **:** Acritamer, Acrylic acid polymer, Carboxy vinyl polymer, carboxypolymethylene.

Chemical name **:** prop-2-enoic acid.

Molecular formula **:** $C_3H_4O_2$

Structure **:**



Molecular weight **:** 700 000 to 4 billion.

Functional category **:** Bioadhesive material, emulsifying agent, suspending agent, stabilizing agent, control-release agent, tablet binder, viscosity-enhancing agent.

Description **:** White colored, fluffy, acidic, hygroscopic powder with slightly characteristic odor.

Typical properties

Density **Bulk** **:** 0.2 to 0.4 g/cm^3

Tapped **:** 0.3 to 0.4 g/cm^3

Melting point **:** Within 30 minutes at 260ºC.

Glass transition temperature: 100 to 105ºC.

Specific gravity **:** 1.41

Viscosity **:** 38850 Cps

Hygroscopicity **:** Typical water content is up to 2% w/w. Typical moisture content at 25ºC and 50% relative humidity is 8 to 10% w/w.

Solubility

It is swellable in water and glycerin and after neutralization in ethanol 95%. They do not dissolve but merely swell to a remarkable extent.

Stability

Carbomers are stable, hygroscopic materials that may be heated at temperature below 104ºC for up to 2 hours without affecting their thickening efficiency. Microorganisms may grow in unpreserved aqueous dispersions.

Storage

In an airtight, corrosion-resistant container and protected from moisture. The use of glass, plastic, or resin-lined containers is recommended for the storage.

Incompatibilities

Incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. They also form pH-dependent complexes with certain polymeric excipients.

Safety

It is essentially nontoxic and nonirritant material. Low oral toxicity is observed. No evidence in humans of hypersensitivity reactions.

Regulatory status

It is included in FDA Inactive Ingredients Guide. Included in Canadian list of Acceptable Non-medicinal ingredients.

Applications

As rheology modifiers, controlled release agents or binders, emulsifying agents, viscosity-increasing aid, and also used in cosmetics.

5.2.2 HYDROXY PROPYL METHYL CELLULOSE[30]

Non-Proprietary Names: BP : Hypromellose,

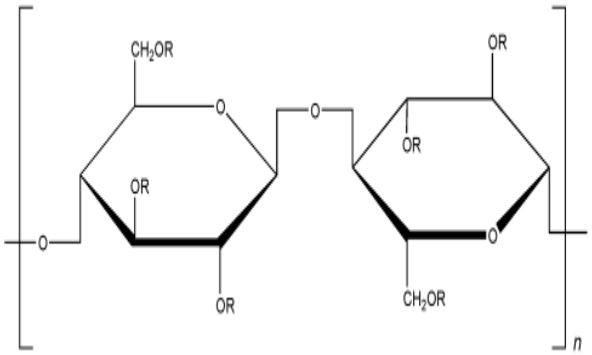
USP: Hydroxy propyl methyl cellulose,

Synonyms **:** Methyl hydroxyl propyl cellulose, propylene glycol ether of methyl cellulose, methylcellulose, methylcellulose propylene glycol ether.

Chemical Name **:** Cellulose, 2-Hydroxypropyl-Methyl Ether

Empirical Formula **:** $C_8H_{15}O_6 – (C_{10}H1_8O_6)_N – C_8H_{15}O_5$

Structure



Molecular Weight **:** Approximately 10,000–1,500,000.

Density **:** 0.25 – 0.70 g/cm^3

Functional Category

Coating agent, film former, tablet binder, viscosity increasing agent, stabilizing agent, suspending agent.

Solubility

Soluble in cold water forming viscous colloidal solution, insoluble in chloroform, ethanol and ether, But Soluble n mixtures of ethanol and methylene chloride.

Viscosity (dynamic)

Methocel Product	**USP 28 Designation**	**Nominal Viscosity(Mpas)**
HPMC 5cps	2208	5000
Methocel K100M	2208	100000

Stability and Storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in airtight container in a cold and dry place. Increase in temperature reduces the viscosity of the solution.

Safety

It is widely used in many oral and topical pharmaceutical formulations. It is generally regarded as a non-toxic and non-irritant material, although excessive consumption may have laxative effect.

5.2.3 HYDROXY ETHYL CELLULOSE[31]

Nonproprietary Names

BP: Hyroxy ethyl cellulose

USP: Hydroxy Ethyl cellulose

Synonyms **:** Alcoramnosan

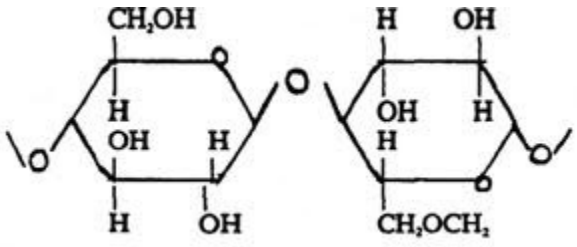
Cellosize

Cellulose hydroxyl ethyl ether

HEC.

Chemical name **:** Cellulose-2-hydroxy ethyl ether.

Structural formula:



Functional category: Coating agent, suspending agent, tablet binder, thickening agent, viscosity increasing agent.

Descriptions **:** It occurs as a light tan or cream to white coloured odorless and Tasteless powder.

Typical properties

Acidity/Alkalinity **:** pH 5.5-8.5 for a 1%w/v aqueous solution.

Density (bulk) **:** 0.35-0.61 g/cm^3

Melting point : Softens at 135-140 degree Celsius, decomposes at about 205 degree Celsius.

Moisture content : Commercially available grades contain less than 5 %w/w of water.

Solubility

It is soluble in either hot or cold water, forming clear, smooth, uniform solutions. Practically insoluble in acetone, ethanol, ether, toluene and most other organic solvents.

Applications

Hydroxy ethyl cellulose is a non ionic, water soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic and topical formulations.

Stability and Storage conditions

It should be stored in a well closed container, in a cool, dry, place.

5.2.4 POLYVINYLPYRROLIDONE[32]

Synonyms : Poly [1-(2-oxo-1-pyrrolidinyl) ethylene]

Polyvidone; polyvinylpyrrolidone,

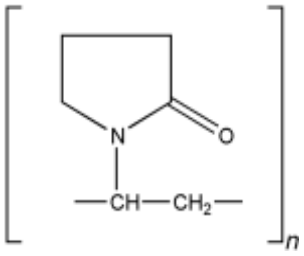
PVP,

1-vinyl-2-pyrrolidinone polymer.

Chemical Name : 1-Ethenyl-2-pyrrolidinone homopolymer.

Empirical Formula: $(C_6H_9NO)_n$

Structural Formula



Molecular Weight : 2500–3 000 000.

Description : Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless.

Typical Properties

Acidity/alkalinity

pH : 3.0–7.0 (5% w/v aqueous solution).

Melting point : Softens at 150°C.

Moisture content

Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Solubility

Freely soluble in acids, chloroform, ethanol (95%), ketones, ethanol, and water; practically insoluble in ether hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, Which is a function of the *K*-value.

Viscosity (dynamic)

The viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

Functional Category

Disintegrant; dissolution aid; suspending agent; tablet binder.

6.2.5 ETHYL CELLULOSE[33]

Nonproprietary Names

BP : Ethylcellulose

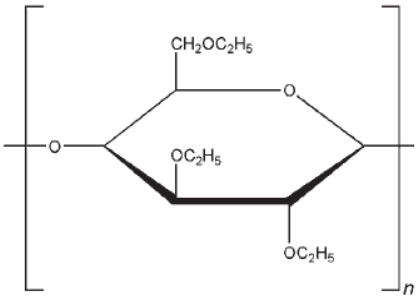
USP : Ethyl cellulose

Synonyms : Aquacoat ECD, Aqualon, Ashacel, Ethocel, ethylcellulosum.

Chemical name : 2-[4,5-diethoxy-2-(ethoxymethyl)-6-methoxyoxan-3-yl]oxy-6- (hydroxymethyl)-5-methoxyoxane-3,4-diol.

Empirical formula : $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_n\ C_{12}H_{23}O_5$

Structural formula :



Functional Category: Coating agent, flavoring agent, tablet binder, tablet filler, viscosity-increasing agent.

Description : A tasteless, free-flowing, white to light tan-colored powder.

Typical properties

Density **:** (Bulk) 0.4 g/cm^3

Melting Point **:** 165 to 185ºC

Glass transition

Temperature: 129 to 133ºC

Specific gravity **:** 1.12 to 1.15 g/cm^3

Hygroscopicity **:** It absorbs very little water from humid air or during immersion

Incompatibilities **:** With paraffin wax and microcrystalline wax material.

Solubility

Practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains not less than 46.5% of ethoxyl groups in freely soluble in chloroform, 95% ethanol, ethyl acetate, methanol, and toluene.

Stability

Stable and slightly hygroscopic material. It is chemically resistant to alkalis both dilute and concentrated and to salt solutions. It is more sensitive to acidic materials.

Storage condition

It should be stored at a temperature not exceeding 90ºF (32ºC) in a dry area. Do not store next to peroxides or other oxidizing agents.

Regulatory status

It is included in the FDA Inactive Ingredients Guide.

Safety

It is a nontoxic, nonallergenic, and nonirritating material. It is not metabolized, therefore it is a noncaloric substance and not recommended for parenteral products. It may be an irritant to the eyes.

Application in pharmaceutical formulation technology

It is widely used in oral and topical pharmaceutical formulations. In tablets, it is employed as a binder being blended dry or wet granulated. It produces tablets with low friability.

5.3 EXCIPIENT PROFILE

5.3.1 LACTOSE[34]

Synonyms **:** 4-(β-D-galactosido)-D-glucose, Lactochem, Microtose, milk sugar, saccharum lactis.

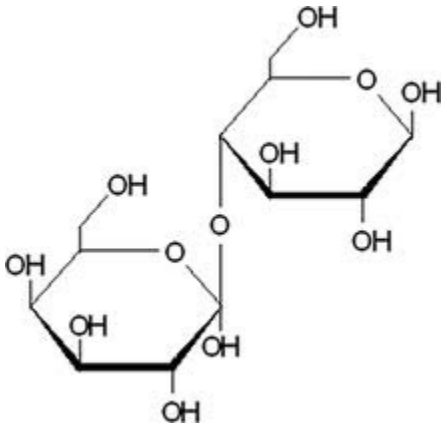
Chemical Name and CAS Registry Number:

o-β-D-Galactopyranosyl-(1-›4)-α-D-glucopyranose anhydrous [63-42-3]

o- β-D-Galactopyranosyl-(1-›4)-α-D-glucopyranose monohydrate [64044-51-5]

Empirical Formula	**Molecular Weight**
$C_{12}H_{22}O_{11}$	342.30 (anhydrous)
$C_{12}H_{22}O_{11}.H_2O$	360.31 (monohydrate)

Structural Formula



Description **:** White to off-white crystalline or powder. Lactose is odor-less and slightly sweet tasting.

Typical Properties

Density **:** 1.540 for α-lactose monohydrate

1.589 for anhydrous β-lactose

Melting Point **:** 201-202°C α-lactose monohydrate

223°C for anhydrous α-lactose

252.2°C for anhydrous β-lactose

Moisture content **:** Anhydrous lactose normally contains up to 1% w/w water.

Functional Category

Tablet and capsule diluent.

Application

Lactose is widely used as a filler or diluent in tablets, capsules, and to a more limited extent in lyophilized products and infant feed formulas.other applications of lactose as a carrier/diluent for inhalation products.

Stability and Storage Conditions

Under humid conditions (80% relative humididity and above) mold growth may occur. The purity of different lactoses can vary and colour evaluation may thus be important. The colour stability of various lactoses alsi differ.

Incompatibilities

A mailard type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown coloured product. This reaction occurs more readily with the amorphous material rather than crystalline lactose.

Safety

Lower doses of lactose produce fewer adverse efffect, and lactose is better tolerated if taken with other food. As a result, there is a significant population with lactose malabsorption who can still ingest normal amount of lactose, such as that in milk, without the development of significant adverse effects.

Materials and Instruments

6. MATERIALS AND INSTRUMENTS

6.1 Table 2: MATERIALS USED

S.NO.	MATERIALS	GRADE	MANUFACTURES / SUPPLIERS
1.	Atorvastatin calcium	Pharma	Dr. Reddy's Laboratories, Ltd, Hyderabad.
2.	Carbopol 934 P	Pharma	Loba Chemie Pvt. Ltd. Mumbai
3.	HPMC K100M	Pharma	Colorcon Asia Pvt. Ltd.
4.	Hydroxy ethyl cellulose	Pharma	Loba Chemie Pvt. Ltd. Mumbai
5.	Ethyl cellulose	Pharma	SD Fine Chemicals Ltd.
6.	Polyvinylpyrolidone	Pharma	Loba chemie pvt.ltd, Mumbai
7.	Lactose	A.R.	Loba Chemie Pvt. Ltd. Mumbai

6.2 Table 3: INSTRUMENTS USED

Sr. No.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1.	Digital Balance	Shimadzu ELB 300
2.	Tablet hardness tester	Monsanto tablet hardness tester.
3.	Friability tester	Electrolab ET-2 friability test apparatus, India.
4.	Dissolution apparatus USP XXIII	Veego tablet dissolution apparatus, Chennai.
5.	Double beam UV Spectrophotometer	Perkin Elmer Lambda - 25 UV/VIS spectrometer
6.	Tablet punching machine	Chamunda Pharma Machinery Pvt.Ltd, Ahmedabad
7.	pH meter	Hanna Instruments, Japan
8.	FT-IR Spectrophotometer	Perkin Elmer spectrum RX1 FT-IR spectrometer.

Methodology

7. METHODOLOGY

7. Preformulation Studies:

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included compatibility studies.

A) Compatibility Studies[35,36]

One of the major requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FTIR spectrometer to find out any possible chemical interaction of atorvastatin calcium with carbopol 934P, HPMC K100M, Hydroxy ethyl cellulose and Polyvinylpyrolidone. Compatibility with excipients was confirmed by FTIR studies.

- **Fourier transform infrared spectrometry (FTIR)**:

Compatibility study of drug with the excipient was determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug with other ingredients in the formulations were compared with that of the original spectra.

7.1 PREPARATION OF STANDARD CALIBRATION CURVE OF ATORVASTATIN CALCIUM[37,38]

Method:

Atorvastatin calcium can be estimated spectrophotometrically at 248 nm.

PREPARATION OF pH 6.8 BUFFER (PHOSPHATE BUFFER)

Dissolve 28.80 gms of disodium hydrogen phosphate and 11.45 gms of potassium dihydrogen phosphate in sufficient water to produce 1000ml.

PREPARATION OF STANDARD SOLUTION FOR CALIBRATION CURVE

10 mg Standard Atorvastatin calcium was accurately weighed and transferred to 100 ml volumetric flask and was dissolved properly and diluted up to the mark with methanol to produce a stock solution of 100 µg/ml. Then 2.5ml of this solution was diluted to 50ml with methanol. Appropriate amount of this stock solution were diluted with the same solvent, yields concentrations of 5µg/ml, 10µg/ml, 15µg/ml 20µg/ml and 25µg/ml which were used for the construction ofcalibration curve.

Table 4: STANDARD CURVE DATA FOR ATORVASTATIN CALCIUM IN pH 6.8 PHOSPHATE BUFFER

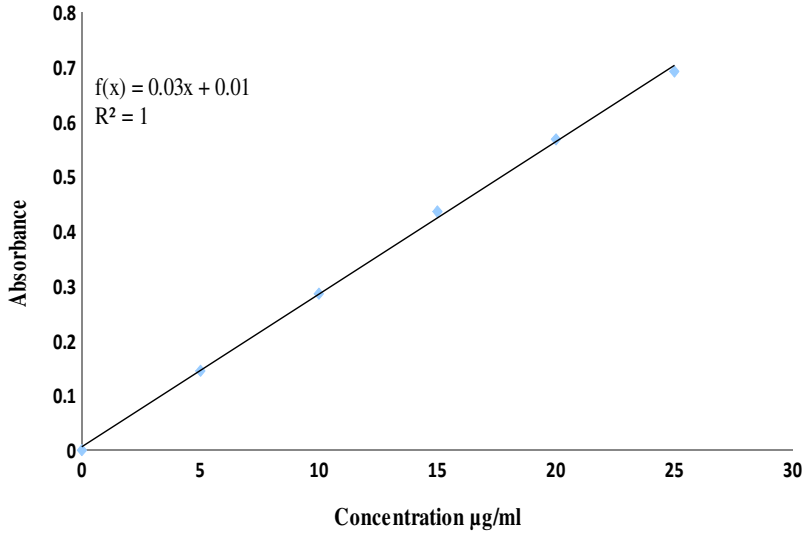
S.No	Concentration In µg/ml	Absorbance at 248 nm
1	5	0.145
2	10	0.286
3	15	0.436
4	20	0.568
5	25	0.692

The linear regression analysis was done on absorbance data points.

(Y = mx+c)

Where ***Y***= Absorbance, ***m*** = slope, ***x*** = Concentration, ***c*** = Intercept.

Fig 4: STANDARD CURVE FOR ATORVASTATIN CALCIUM IN pH 6.8 PHOSPHATE BUFFER



Slope=0.027

R^2=0.999

7.2 PREPARATION OF MUCOADHESIVE BUCCAL TABLETS OF ATORVASTATIN CALCIUM

Mucoadhesive buccal tablets containing atorvastatin calcium were prepared by direct compression method. The ingredients of the core layer (table:5) were weighed accurately and mixed by trituration in a glass mortor & pestle. The mix was then compressed using 8 mm die by a tablet press. In order to obtain constant tablets weight the spray dried lactose was added as filler excipient in the core layer. After compression of tablet the upper punch was removed carefully without disturbing the set up and mixed ingredients of the backing layer were added over the tablet and compressed again.

Table 5: composition of mucoadhesive buccal tablets of atorvastatin calcium

Ingredients (mg)	Batch I			Batch II			Batch III		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
ATR	10	10	10	10	10	10	10	10	10
Carbopol 934	20	20	20	25	25	25	30	30	30
HPMC K100M	15	20	25	15	20	25	15	20	25
HEC	15	10	5	15	10	5	15	10	5
PVP 30	6	6	6	6	6	6	6	6	6
Lactose (sd)	54	54	54	49	49	49	44	44	44
Backing layer	40	40	40	40	40	40	40	40	40

Drug - Atorvastatin calcium

HPMC K100M - Hydroxy propyl methyl cellulose

HEC - Hydroxy ethyl cellulose

PVP - Polyvinylpyrolidone 30

Backing Lay : Ethyl cellulose

7.3 PHYSICOCHEMICAL EVALUATION OF MUCOADHESIVE BUCCAL TABLETS

I) Pre-Compression Parameters[39]

A) Angle of repose:

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$$\theta = \tan^{-1} (h/r)$$

Where, h = height, r = radius, θ = Angle of repose

Procedure:

5 grams of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the above formula. This was repeated five times for a sample.

B) Determination of bulk density and tapped density

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas

Bulk density = W / V_O and Tapped density = W / V_f

Where, W = weight of the powder

V_O = initial volume

V_f = final volume

C) Compressibility index (Carr's indices):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 to 30% is defined as the free flowing material. The limits are mentioned in the table no 6**.**

$$C_I = 100(V_O - V_f)/V$$

Table No: 6

% Comp. Index	**Properties**
5-12	Free flowing
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

D) Hauser's Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hauser's Ratio = $(W / V_f) / (W / V_0)$ where,

W / V_f = Tapped density and W / V_0 = Bulk density.

Thus,

Hauser's Ratio = Tapped density/Bulk density

Table No: 7

S. No.	**Hauser's Ratio**	**Property**
1.	0-1.2 43	Free flowing
2.	1.2-1.6	Cohesive powder

II) Post-Compression Parameters[34]:

A) Shape of Tablets:

The compressed tablets were examined under the magnifying lens for the shape of the tablet.

B) Tablet Dimensions:

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

C) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

D) Friability Test:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w). The % friability was then calculated by

$$\textbf{Percentage of Friability} = 100\ (1-w_0/w)$$

Percentage friability of tablets less than 1% is considered acceptable.

E) Weight Variation Test:

Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table and none deviates by more than twice the percentage. USP official limits of percentage deviation of tablet are presented in the table no : 8.

Table 8: Weight Variation Tolerances for Uncoated Tablets

S. No.	Average weight of Tablets (mg)	Maximum percentage difference allowed
1.	130 or Less	10
2.	130 to 324	7.5
3.	More than 324	5.0

$$\% \text{ Maximum positive deviation} = (W_H - A / A) \times 100$$

$$\% \text{ Minimum negative deviation} = (A - W_L / A) \times 100$$

Where, W_H = Highest weight in mg.

W_L = Lowest weight in mg.

A = Average weight of tablet in mg

F. Drug Content Uniformity[40]

5 Tablets were weighed, and an accurately weighed sample of powdered tablets equivalent 10mg of ATR [equivalent to one tablet]. Quantity of powder equivalent to 10

mg of ATR was weighed and dissolved in 60 ml of methanol and sonicated for 10 minutes in a 100ml volumetric flask and this solution was filtered through Whatmann No.1 filter paper. The residue was washed with 10ml methanol three times and volume made upto 100ml with methanol. The solution obtained was diluted with the Methanol. All determinations were carried out in three replicates. ATR were determined by measuring the absorbance of the sample at 246 nm. Amount of drug present was determined from the standard curve of atorvastatin calcium in methanol.

G. Mucoadhesion Strength[41,42,43]

Bio-adhesive strength of the tablets was measured on a modified physical balance. The method used goat cheek pouch as the model mucosal membrane (a non keratinized epithelium, comparable to human buccal mucosa) and pH 6.8 as the moistening fluid. The two working of a double beam physical balance formed the basis of the bioadhesion test apparatus fabricated. The right pan was replaced with chain setup with adhesive plate. The height of this total setup was adjusted to accommodate a glass container. This setup was kept inside the glass container and the sides were balanced. The setup with tablet was attached with mucosa in container, which was filled with isotonic phosphate buffer (pH 6.8) kept at 37±1˚C.

The balance was kept in this position for 3 min and then slowly weights are increased on the right pan, till the tablet separated from the mucosal surface. The weight, in gms, required to detach the tablets from the mucosal surface gave the measure of bio-adhesive strength. Not more than 3 tablets were tested on each mucosal membrane. After each measurement tissue washed with phosphate buffer (pH 6.8).

H. Swelling Index[44, 45]

The swelling properties and the erosion characteristics of tablets were evaluated by determination of the percentage of hydration and matrix erosion or dissolution (DS). The percent values were calculated according to the following equations:

$$\text{Percentage of swelling} = (W2 - W1)\, W2 * 100$$

Each tablet was weighed (W1) and immersed in phosphate buffer at pH 6.8 for predetermined times (1, 2,3,4,5,6,7,8,9,10,11,12 hours). After immersion, excess surface water was removed from the tablets using filter paper and weighed (W2). The swollen tablets were dried at 60°C for 24 hours in an oven and kept in a desiccator for 48 hours prior to reweighing (W3). This experiment was performed in triplicate.

I. Measurement of Surface pH[46, 47, 18]

A combined glass electrode was used for this purpose. The buccal tablets were kept in contact with 0.5 ml of distilled water for 1 h. pH was noted by bringing the electrode near the surface of the formulations and allowing it to equilibrate for 1 min.

J. In Vitro Dissolution Studies[48,49,50]

Dissolution parameters:

Medium **:** pH 6.8 phosphate buffer

Apparatus **:** USP - Type II (paddle)

RPM **:** 50

Temperature **:** 37° ± 0.5° C

Medium volume: 500 ml

In vitro release studies: The drug release rate from buccal tablets was studied using the USP 28 type II dissolution test apparatus. To release the drug from one side the

impermeable backing layer side of the tablet was fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 mL of phosphate buffer pH 6.8. The release was performed at 37±0.5°C, with a rotation speed of 50 rpm. Samples of 1ml were collected at different time intervals up to 12 h and analyzed spectrophotometrically at 246 nm.

k. Ex vivo Buccal Permeation studies[46]

Porcine buccal tissue from domestic goat was obtained from a local slaughter house and used within 2 hours of slaughter. The tissue was stored in phosphate buffer pH 6.8 at 40 C after collection. The epithelium was separated from the underlying connective tissue with a surgical technique and delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity.

Ex vivo permeation study of atorvastatin buccal tablets through the goat buccal mucosa was performed using Franz-type diffusion cell. The freshly excised goat buccal mucosal membrane was clamped between donor and receiver chambers of the Franz-type diffusion cell, facing the mucosal side towards the donor compartment. The receiver chamber was filled with fresh pH 6.8 buffer solution and after the buccal membrane was equilibrated for 30 min. The buccal tablet was placed in donor chamber and the receptor compartment was maintained at 37±0.20C and continuously stirred at 50 rpm throughout the study.

Aliquots (1ml) were collected at predetermined time intervals and filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 246 nm using a UV spectrophotometer. The medium of the same volume (1ml), which was prewarmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate.

l.kinetics of drug release

In order to understand the mechanism and kinetics of drug release, the drug release data of the in vitro dissolution study were analyzed with various kinetics models like Zero order, first order, Higuchi's and peppa's. Coefficient of correlation was calculated for the linear curves obtained by regression analysis.

Fitting of Results into Different Kinetic Equations[48, 49]:

The results of in- vitro and ex vivo release profile obtained for all the formulations were plotted in modes of data treatment as follows: -

1. Zero - order kinetic model - Cumulative % drug released Vs time.
2. First – order kinetic model - Log cumulative percent drug remaining Vs time.
3. Higuchi's model - Cumulative percent drug released Vs square root of time.
4. Korsmeyer equation / Peppa's model - Log cumulative percent drug released Vs log time.

A) Zero order kinetics:

Zero order release would be predicted by the following equation: -

$$A_t = A_0 - K_0 t$$

Where, A_t = Drug release at time 't'.

A_0 = Initial drug concentration.

K_0 = Zero - order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order equal to K_0.

B) First Order Kinetics:

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - Kt / 2.303$$

Where , C = Amount of drug remained at time 't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

C) Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation: -

$$Q = [D\varepsilon / \tau (2 A - \varepsilon Cs) Cst]^{½}$$

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which ‘q’ amount of drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’ and ‘A’ are constant. Then equation becomes: -

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘K’ (Higuchi’s 1963).

D) Korsmeyer equation / Peppa’s model:

To study the mechanism of drug release from the sustained-release matrix tablets of Ciprofloxacin, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa’s law equation), which is often used to describe the drug release behavior from polymeric systems.

$M_t / M_\alpha = Kt^n$ Where,

M_t / M_α = the fraction of drug released at time ‘t’.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get: -

$$\text{Log } M_t / M_\alpha = \text{Log } K + n \text{ Log } t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non - Fickian) transport 'n' ranges between 0.5 and 1.0.

Table 9: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S. No.	n Value	Drug release
1.	0.45	Fickian release
2.	0.45 < n <1.0	Non – Fickian release
3.	1.0	Class II transport

Curve Fitting of Release Profile:

The in- vitro dissolution data were fitted to the Korsmeyer and Peppa's equation

$$\mathbf{Mt/M\infty = kt^n}$$

where Mt/M∞ represents the fraction of drug release at time t, k is the release rate constant, and n is the diffusion coefficient. The entire curve-fitting analysis was performed using GraphPad Prism version 3.02 (GraphPad Software,Inc) and Excel (Microsoft) software.

Results

9. RESULTS

In order to achieve the development of mucoadhesive buccal tablet dosage forms, Atorvastatin calcium was used as a model drug. Mucoadhesive buccal tablets were formulated by direct compression method employing carbopol 934 P, HPMC K100M and hydroxy ethyl cellulose in different ratios.

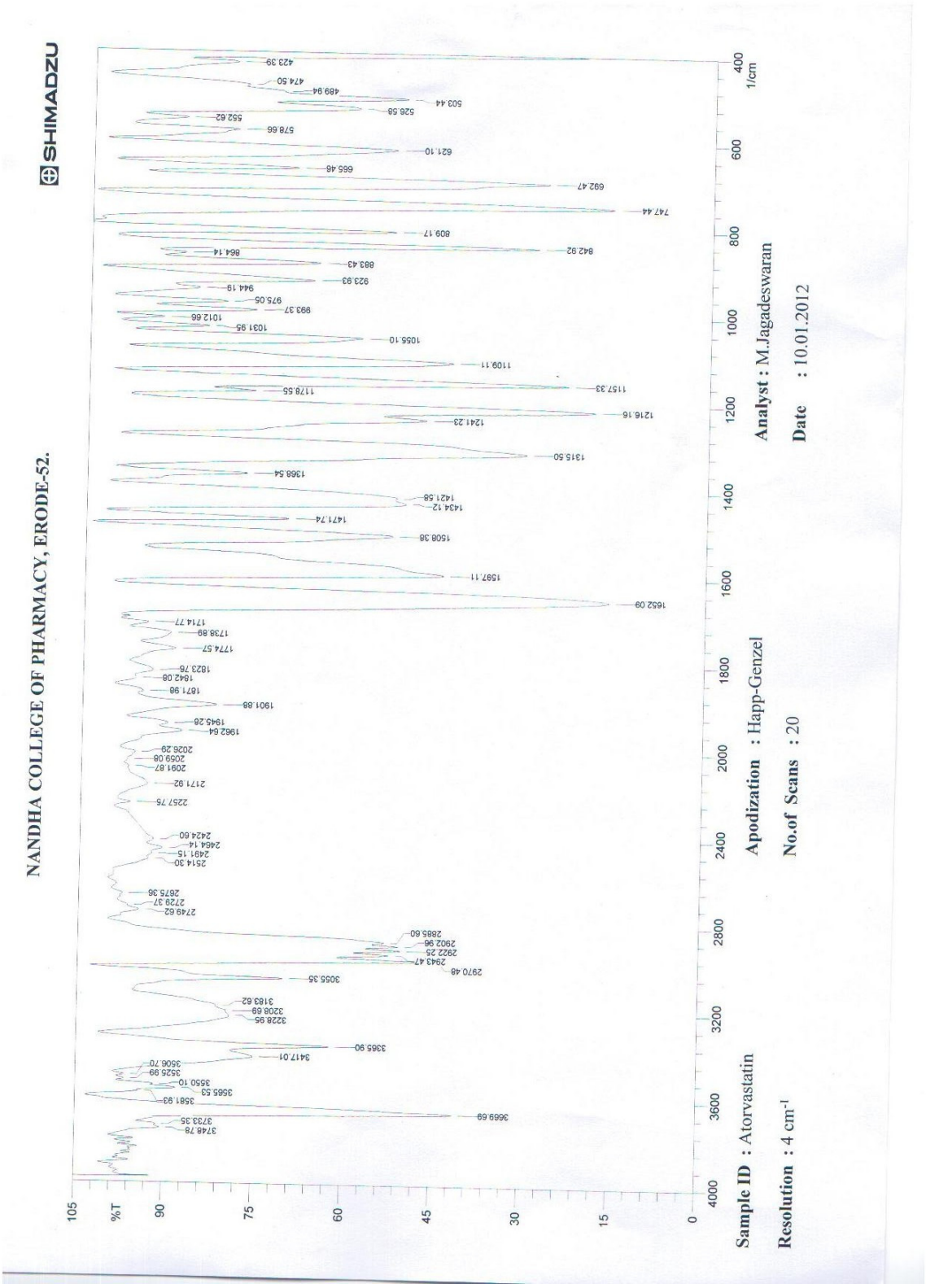
In the present study nine formulations (F1-F9) were prepared by using carbopol 934 P, HPMC K100M and Hydroxy ethyl cellulose. To know the mechanism of drug release from these formulations, the data were fitted in various kinetic models like zero order plot, first-order plot, Higuchi's plot, and Korsmeyer equation / Peppa's model et al's equations.

The results related to physicochemical, in- vitro evaluation and ex-vivo evaluation of mucoadhesive buccal tablets of atorvastatin calcium are given in Table: 15 – 28.

8.1 Preformulation Studies (Compatibility Studies):

Compatibility studies were performed by using FT-IR spectrophotometer. The IR Spectrum of pure me Atorvastatin Calcium drug was compared with the IR spectrum of physical mixture of Atorvastatin Calcium with Carbopol, Hydroxy propyl methyl cellulose K100M, Hydroxy ethyl cellulose, PVP and other excipients.

There was no appearance or disappearance of any characteristics peaks related to the drug. This shows that there is no chemical interaction between the drug and the polymers.


SHIMADZU
NANDHA COLLEGE OF PHARMACY, ERODE-52.
%T
1/cm
Sample ID : Atorvastatin
Resolution : 4 cm-1
Apodization : Happ-Genzel
No.of Scans : 20
Analyst : M.Jagadeswaran
Date : 10.01.2012

NANDHA COLLEGE OF PHARMACY, ERODE-52.

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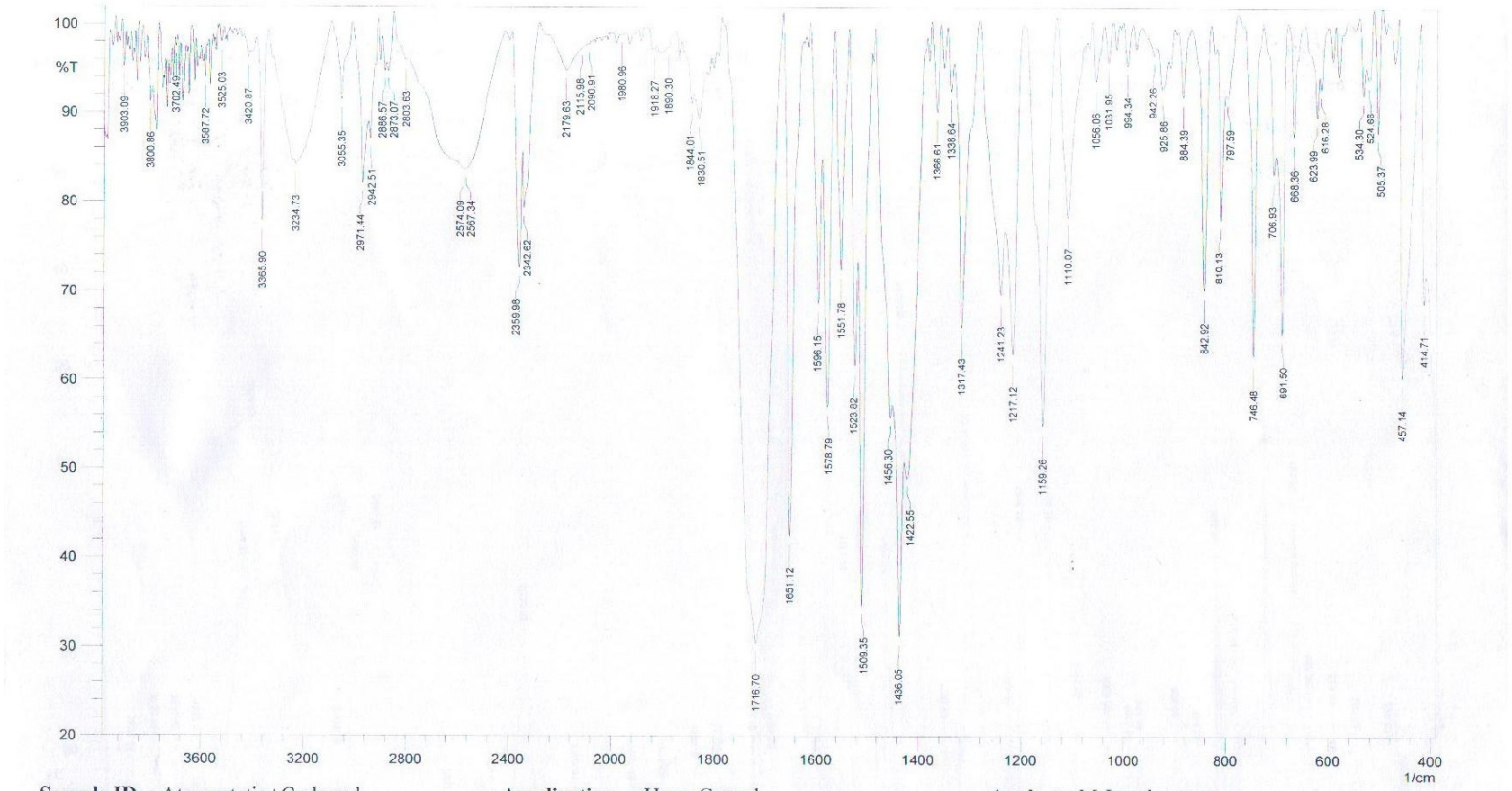

Sample ID : Atorvastatin+Carbopol **Apodization** : Happ-Genzel **Analyst :** M.Jagadeswaran

Resolution : 4 cm^{-1} **No.of Scans** : 20 **Date** : 21.03.2012

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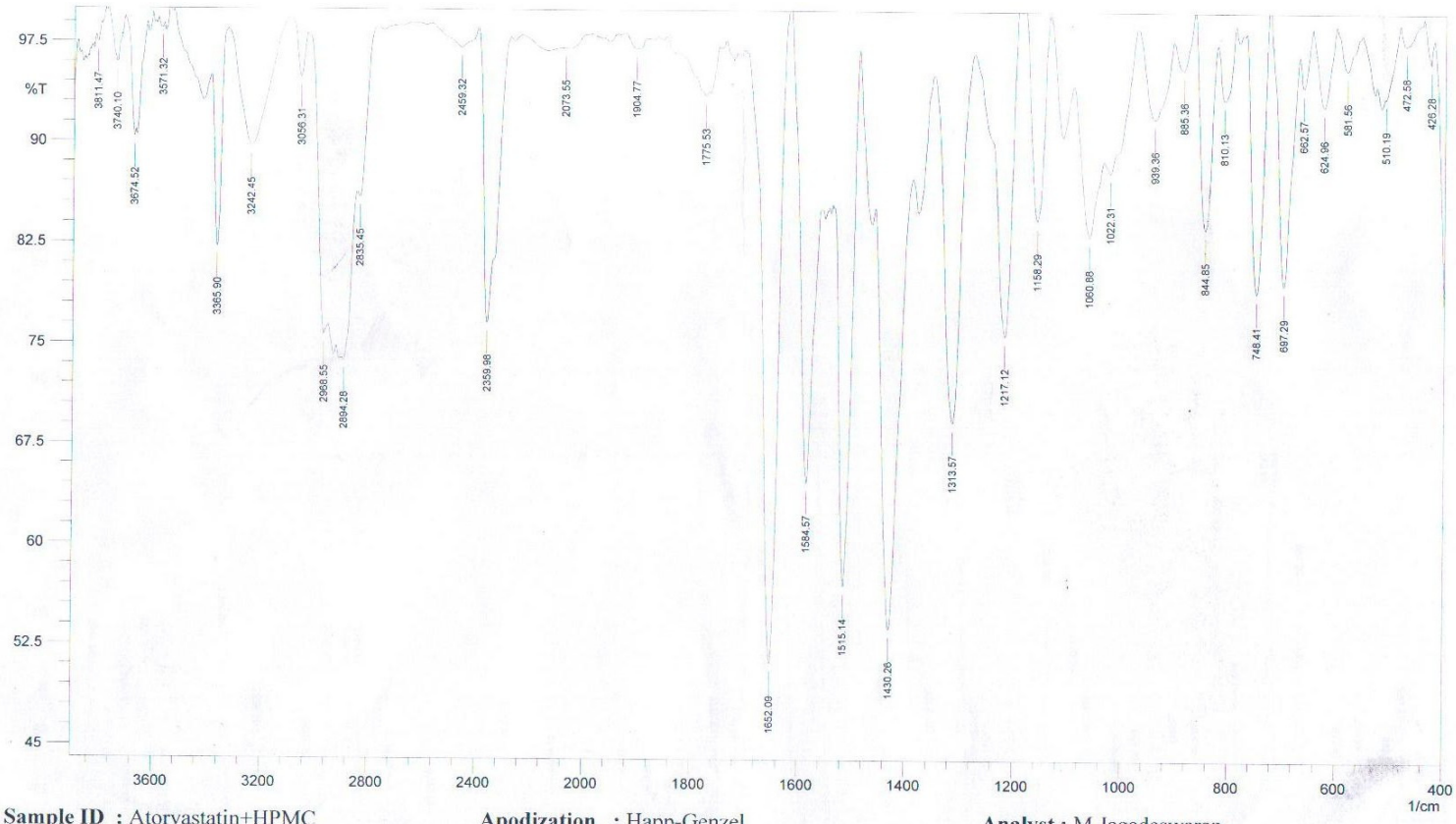

Sample ID : Atorvastatin+HPMC

Apodization : Happ-Genzel

Analyst : M.Jagadeswaran

Resolution : 4 cm^{-1}

No.of Scans : 20

Date : 21.03.2012

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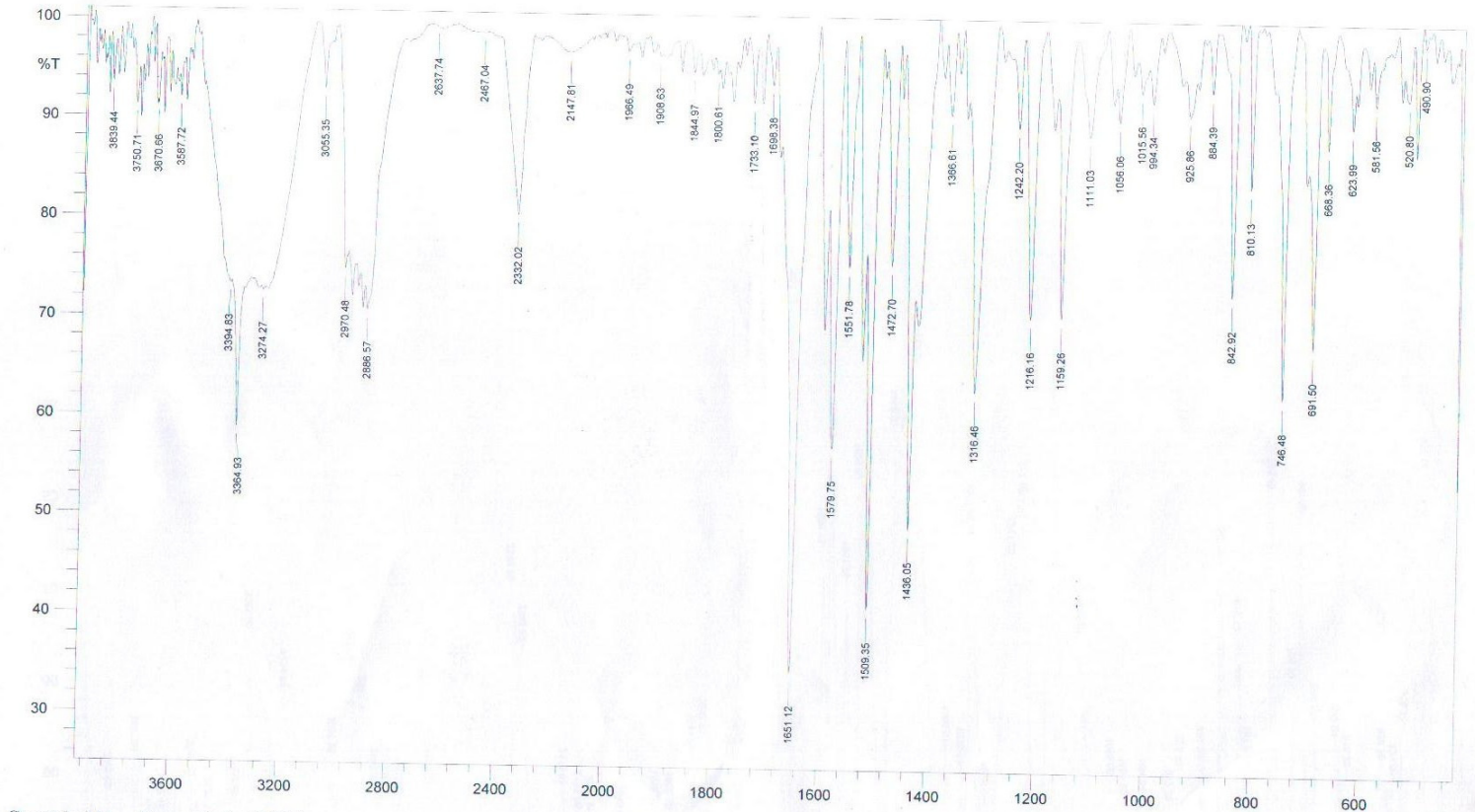

Sample ID : Atorvastatin+HEC

Apodization : Happ-Genzel

Analyst : M.Jagadeswaran

Resolution : 4 cm^{-1}

No.of Scans : 20

Date : 21.03.2012

NANDHA COLLEGE OF PHARMACY, ERODE-52.

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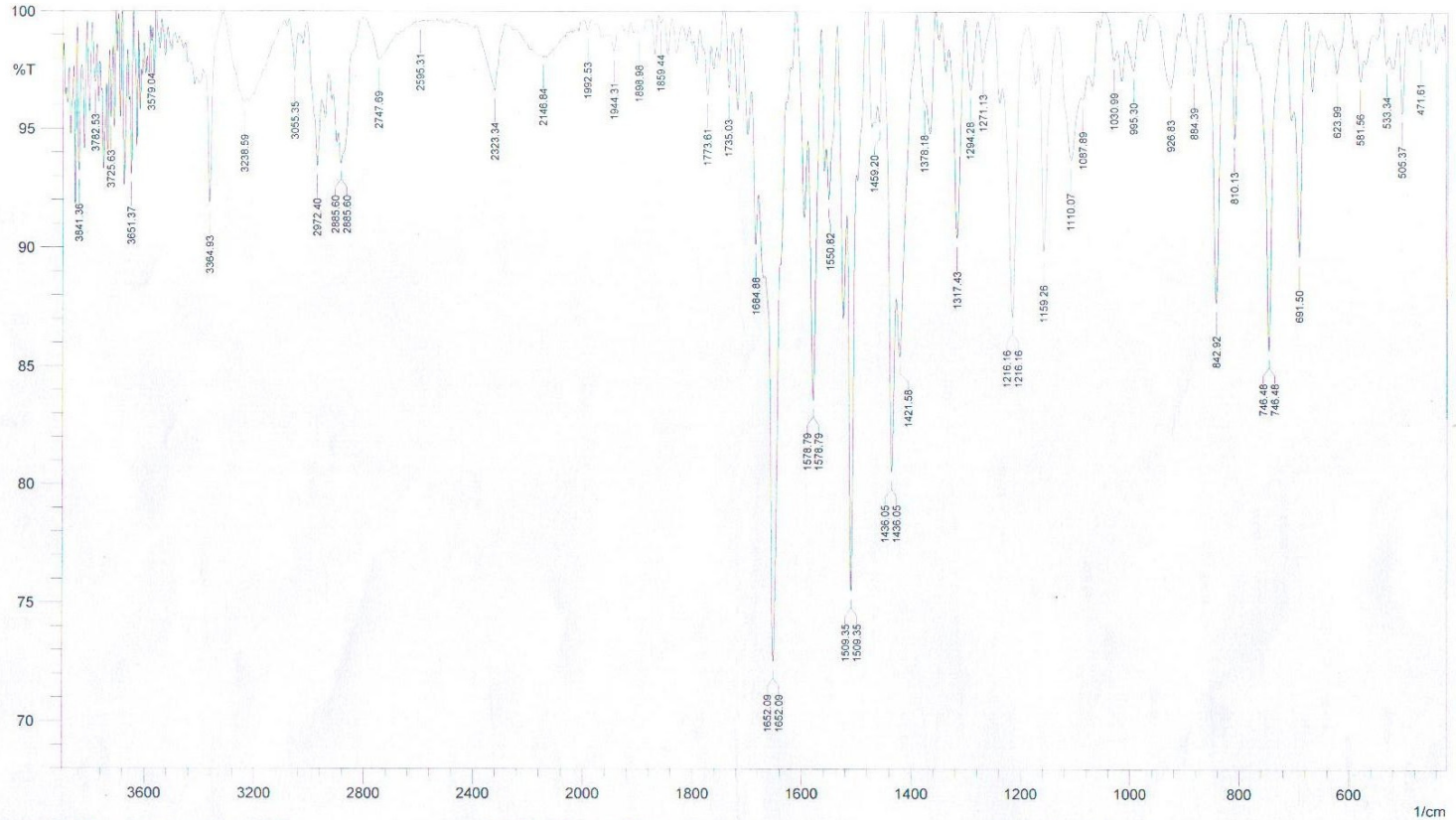


Sample ID : Atorvastatin+PVP **Apodization** : Happ-Genzel **Analyst** : M.Jagadeswaran

Resolution : 4 cm^{-1} **No.of Scans** : 20 **Date** : 21.03.2012

2.2 EVALUATION OF BLEND CHARACTERISTICS OF ATORVASTATIN CALCIUM

I) Pre-compression parameters:

The powder blends of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, and Hauser's ratio. The results of these evaluations are as follows: -

a) Angle of Repose (θ):

The angle of repose for the formulated blend was carried out and the results were shown in the table. It concludes the entire formulation blend was found to be in the range $31^0 45' \pm 0.1210$ to $34^0 02' \pm 0.4347$. The values are in Table No: 10.

b) Bulk Density:

Bulk density is used for the measurement of Compressibility index. The bulk density ranged from 0.431±0.0005 to 0.343±0.0080 respectively. The values are in Table No: 11.

c) Tapped Density:

Tapped density is used for the measurement of Compressibility index. The tapped density ranged from 0.506±0.506 to 0.425±0.0066 respectively. The values are in Table No: 12.

d) Compressibility Index: -

Compressibility index was carried out, it is found between 19.280±1.201 to 13.760±1.021. The values are mentioned in Table: 13.

e) Hauser's Ratio:

The Hauser' ratio ranged from 1.238 ± 1.018 to 1.159± 0.013. The values are mentioned in Table: 14.

Table 10: Physical Characteristics of Atorvastatin calcium Powder Blend

F.Code	Angle of repose(°) Mean ± S.D	Bulk density (gm/cc) Mean±S.D	Tapped density (gm/cc) Mean±S.D	Compressibility Index Mean ± S.D	Hausner's Ratio Mean±S.D
F1	32˚05' ± 0.428	0.388 ± 0.0081	0.45 ± 0.0041	14.707 ± 0.482	1.172 ± 0.006
F2	32˚26' ± 0.189	0.386 ± 0.0052	0.459 ± 0.0015	14.803 ± 0.935	1.173 ± 0.012
F3	34˚ ± 0.392	0.373 ± 0.0016	0.437 ± 0.0126	13.760 ± 1.021	1.159 ± 0.013
F4	33˚18' ±0.0802	0.431 ± 0.0005	0.506 ± 0.506	14.797 ± 0.855	1.173 ± 0.015
F5	33˚01' ± 0.459	0.386 ± 0.0070	0.473 ± 0.0037	18.511 ± 0.865	1.226 ± 0.012
F6	32˚06' ± 0.551	0.415 ± 0.0050	0.496 ± 0.0050	16.529 ± 0.1222	1.198 ± 0.017
F7	34˚02' ± 0.434	0.362 ± 0.0017	0.440 ± 0.0218	18.318 ± 0.789	1.215 ± 0.015
F8	31˚45' ± 0.121	0.413 ± 0.0026	0.501 ± 0.0030	17.671 ± 0.848	1.214 ± 0.012
F9	32˚39' ± 0.190	0.343 ± 0.0080	0.425 ± 0.0066	19.280 ± 1.201	1.238 ± 0.018

8.3 Physical evaluation parameter of mucoadhesive buccal tablets of Atorvastatin calcium

Atorvastatin calcium mucoadhesive buccal tablets were evaluated for various physical parameters – Hardness, thickness, Friability, Weight variation, diameter etc.

8.3.1 Thickness:

The thickness of all batches ranged from 3.49±0.005 to 3.21±0.010 mm as shown in the Table -16.

8.3.2 Diameter:

The diameter of all batches ranged from 3.49±0.005 to 3.21±0.010 mm as shown in the Table -16.

8.3.3 Hardness Test:

The hardness of all batches ranged from 5.1 to 5.6 kg/cm^2 as shown in the Table -15.

8.3.4 Friability Test:

The percentage friability of all batches ranged from 0.361 % to 0.464 % as shown in the Table-17.

8.3.5 Weight Variation Test:

The percentage weight variations for all formulations are performed. All the formulations (F1-F9) passed weight variation test as per the Pharmacopoeias limits of 5% as shown in the Table -18.

8.3.6 Drug content uniformity:

Drug content was found to be ranged from 99.01±0.56 to 96.95±0.20 as shown in the Table -19

TABLE 11: POST COMPRESSION PARAMETERS

F Code	Thickness (mm)±SD	Diameter (mm)±SD	Hardness (Kg/cm^2)± SD	Friability (%)±SD	Weight variation (mg) ±SD	% drug content
F1	3.35± 0.011	8.14 ± 0.032	5.2±0.115	0.464 ±0.004	159.7 ±0.493	98.87 ±0.38
F2	3.31± 0.005	8.91 ± 0.109	5.3±0.057	0.413 ±0.002	158.9 ±0.251	99.01 ±0.56
F3	3.40±0.00 5	8.19 ± 0.122	5.6±0.152	0.398 ±0.002	159.1 ±0.700	96.95 ±0.20
F4	3.39± 0.005	8.69 ± 0.124	5.6±0.115	0.394 ±0.004	158.9 ±0.519	97.38 ±0.84
F5	3.49± 0.005	8.24 ± 0.121	5.3±0.115	0.418 ±0.004	158.5 ±0.602	97.38 ±0.65
F6	3.27± 0.015	8.66 ± 0.071	5.5±1.157	0.392 ±0.002	158.7 ±0.472	98.26 ±0.29
F7	3.41± 0.011	8.82 ± 0.233	5.1±0.115	0.405 ±0.003	158.4 ±0.493	97.54 ±0.98
F8	3.21± 0.010	8.96 ± 0.058	5.1±0.100	0.361 ±0.003	158.7 ±0.435	98.62 ±0.52
F9	3.33± 0.015	8.56 ± 0.088	5.4±0.100	0.408 ±0.003	158.9 ±0.602	97.86 ±0.17

8.3.7 Swelling study

Swelling studies were conducted for all formulations and the results were shown in table all the formulations were hydrated generally by keeping the tablets in contact with water for 1hour to 12hours.

Table 12: swelling index profile of formulations

Time hr	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.21	0.26	0.16	0.21	0.27	0.18	0.10	0.22	0.32
2	0.42	0.66	0.48	0.34	0.41	0.35	0.29	0.54	0.63
3	0.84	0.91	0.92	0.56	0.55	0.61	0.56	0.76	0.99
4	1.10	1.01	1.45	0.75	0.88	0.96	0.81	1.08	1.21
5	1.46	1.57	1.73	1.17	1.21	1.45	0.95	1.33	1.46
6	1.95	1.88	1.98	1.38	1.51	1.88	1.14	1.56	1.75
7	2.11	2.22	2.16	1.63	1.90	2.11	1.35	1.98	1.90
8	2.25	2.35	2.31	2.08	2.20	2.38	1.58	2.18	2.06
9	2.35	2.42	2.48	2.32	2.49	2.51	2.01	2.27	2.22
10	2.41	2.46	2.56	2.49	2.55	2.58	2.20	2.36	2.48
11	2.43	2.51	2.61	2.52	2.59	2.63	2.31	2.44	2.56
12	2.48	2.55	2.64	2.54	2.62	2.68	2.38	2.47	2.67

Fig 5: Swelling index Vs Time [F1-F3]

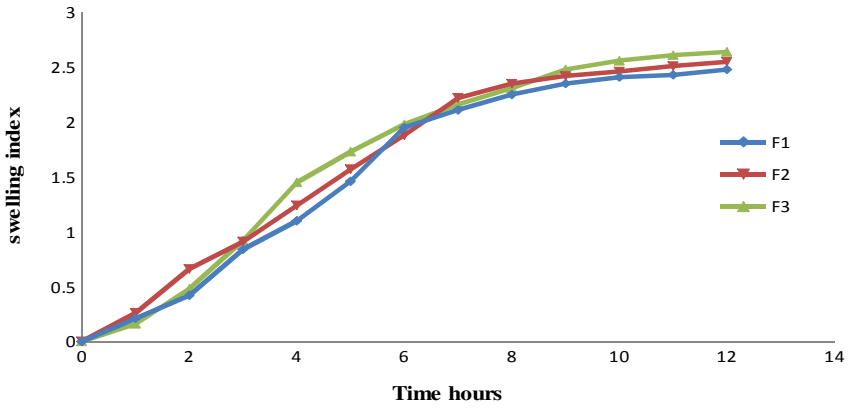


Fig 6 :Swelling index Vs Time [F4-F6]

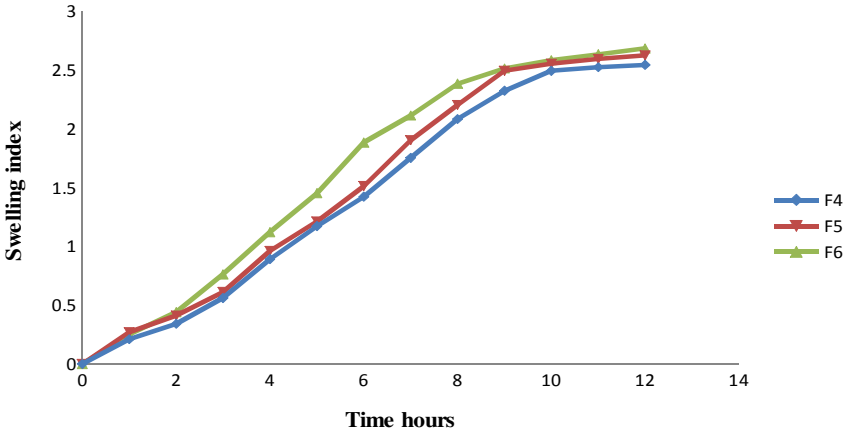


Figure 7: Swelling index Vs Time [F7-F9]

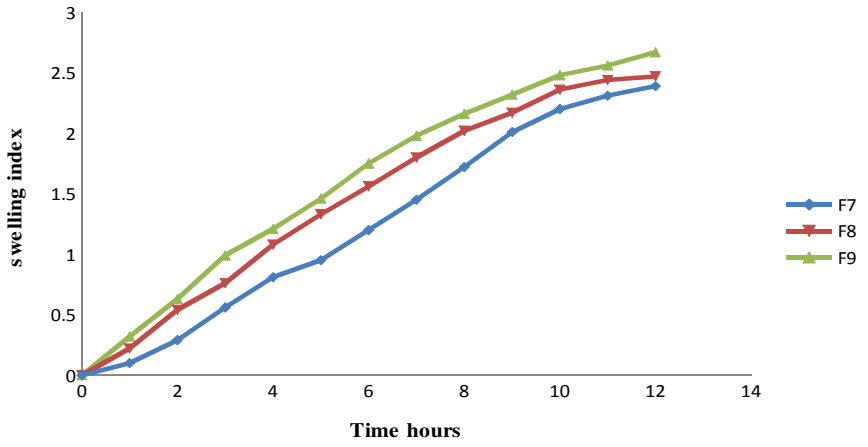


Fig 8: swelling index comparison

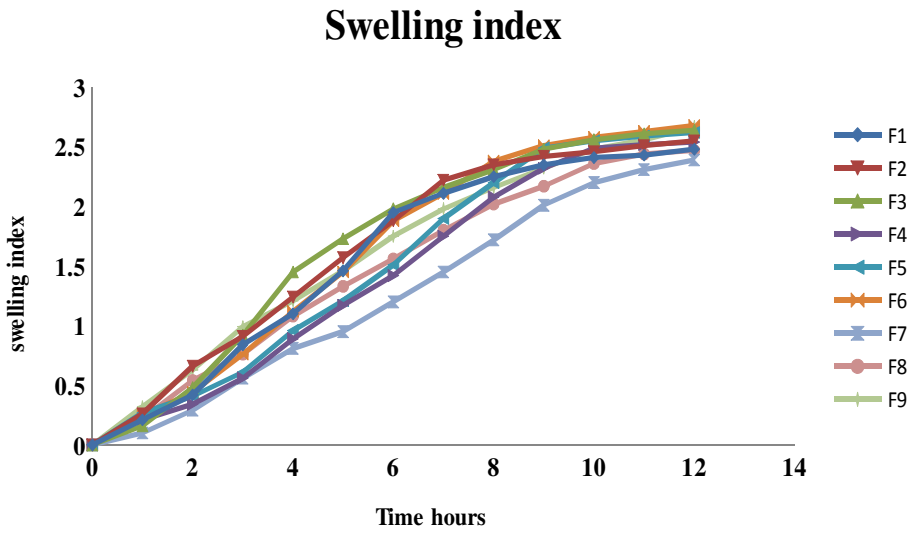
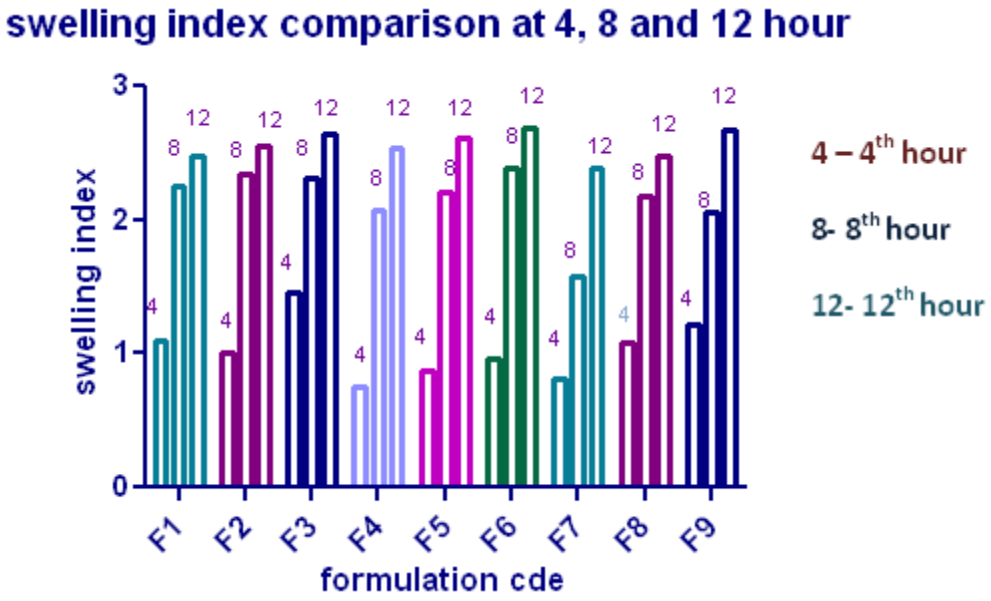


Fig 9: swelling index comparison at 4 hour, 8 hour and 12 hour



8.3.8 Ex vivo Mucoadhesive Strength:

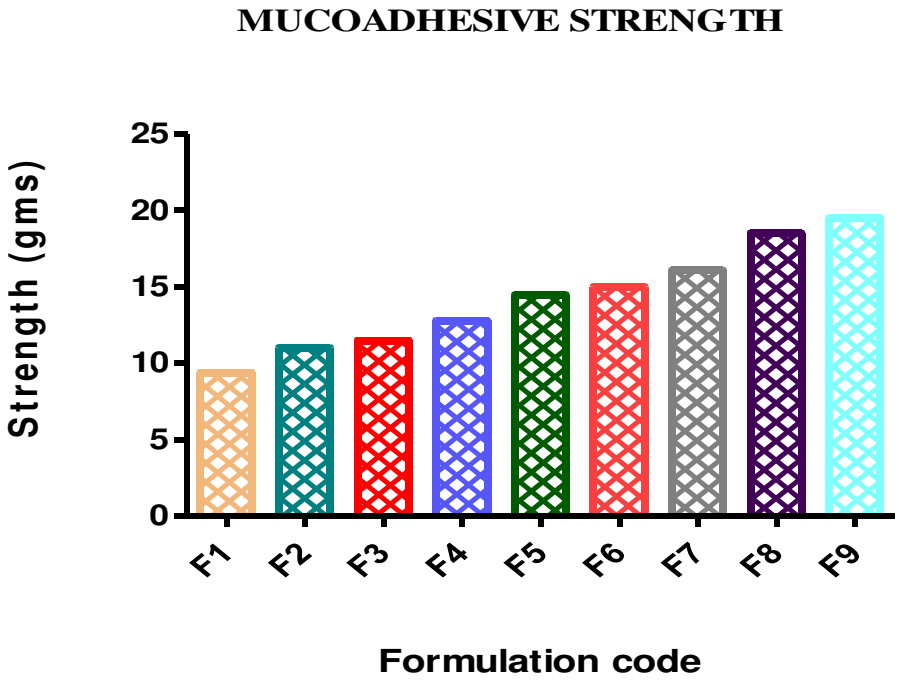
Mucoadhesion studies were carried out by Ex vivo method using freshly obtained goat buccal mucosa without any further treatment. The property of polymer is closely associated with mucoadhesion because polymer swelling depended upon the water inhibition which in turn increases the diffusion and interpenetration of macromolecules. Increasing the total polymer content of formulation induces more adhesion strength. The possible explanation for such behavior is due to high concentration of carpobol upon exposure to the moist surfaces, the pH of the microenvironment became acidic which caused increases in mucoadhesion.

Table 13: Mucoadhesive strength

S.NO	FORMULATIONS	TRIAL I	TRIAL II	TRIAL III	MEAN ± SD

1	F1	9.9	8.9	9.6	9.4±0.51
2	F2	10.9	10.5	11.6	11.03±0.61
3	F3	11.8	12.4	10.5	11.50±0.97
4	F4	13.2	12.8	12.4	12.8±0.40
5	F5	14.8	14.1	14.5	14.46±0.35
6	F6	15.2	16.1	15.7	15.03±0.25
7	F7	15.8	16.3	16.2	16.1±0.26
8	F8	17.9	19.0	18.7	18.53±0.56
9	F9	20.1	18.9	19.6	19.53±0.60

Fig 10: comparison of mucoadhesive strength



In vitro assembly for mucoadhesive strength determination

9.3.9 Measurement of surface pH

The microenvironment pH of the buccal tablets was determined in order to investigate the possibility any side effect in vivo. The another studies demonstrated that a low surface PH caused damage to a contacting mucosal surface. Therefore, it was important in the present study to determine if any extreme surface pH changes occurred with the mucoadhesive buccal tablet development.

Table 14: Measurement of surface pH

S.NO	FORMULATIONS	TRIAL I	TRIAL II	TRIAL III	MEAN	SD
1	F1	6.8	6.4	6.5	6.5	0.208
`2	F2	7.2	7.1	7.0	7.1	0.100

3	F3	7.1	6.9	7.1	7.0	0.115
4	F4	7.0	7.1	7.1	7.0	0.057
5	F5	6.7	6.8	6.9	6.8	0.100
6	F6	6.9	7.0	6.8	6.9	0.100
7	F7	7.2	7.0	7.2	7.1	0.115
8	F8	6.6	6.8	6.6	6.6	0.115
9	F9	6.9	6.7	6.6	6.7	0.152

8.3.10 IN VITRO DRUG RELEASE PROFILE

Release of atorvastatin calcium from the buccal tablets was studied in phosphate buffer pH 6.8 (500 ml) in USP XXIV employing apparatus II. One tablet containing 10 mg of atorvastatin calcium, at paddle speed of 50 rpm and a temperature of 37 ± 0.5°C were employed in each test. Samples were withdrawn through a filter (0.45μ) at different time intervals, suitably diluted and assayed spectrophotometrically at 246 nm using a UV double beam spectrophotometer and drug release compared with various polymer concentrations. Drug release experiments were conducted in triplicates.

In vitro drug release data of all formulations of atorvastatin calcium was subjected to curve fitting analysis according to zero order, first order kinetics and according to Higuchi´s and peppa´s models to ascertain mechanism of drug release.

`

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	17.501	16.852	17.998	17.450±0.574
2	22.484	21.773	21.134	21.797±0.675
3	28.482	28.528	28.794	28.601±0.168
4	35.854	35.652	34.382	35.296±0.798
5	47.936	47.192	46.094	47.074±0.926
6	52.252	52.984	52.189	52.140±0.905
7	57.124	58.232	57.324	57.560±0.590
8	65.688	66.422	66.121	66.077±0.364
9	71.857	70.138	72.212	71.402±1.109
10	78.394	78.644	79.524	78.854±0.593
11	87.346	88.124	87.194	87.554±0.498
12	96.023	95.792	95.184	95.666±0.433

IN

Table No : 15

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F2

Table no: 16

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	15.962	14.681	14.128	14.923±0.940
2	21.884	21.324	21.184	21.464±0.894
3	27.885	26.185	25.554	26.874±0.894
4	32.258	33.184	32.192	32.544±0.554
5	39.089	38.467	38.186	38.580±0.462
6	46.184	47.512	47.782	47.159±0.855
7	55.618	56.915	55.271	55.934±0.866
8	62.194	63.886	62.727	62.935±0.865
9	73.857	74.135	73.293	85.830±0.659
10	86.510	85.192	85.790	85.830±0.659
11	91.145	90.817	91.497	91.153±0.340
12	96.614	96.401	97.124	96.124±96.713

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F3

Table no: 17

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	15.962	14.321	15.618	15.300±0.865
2	21.384	21.861	22.424	21.889±0.520
3	27.881	27.184	28.713	27.926±0.765
4	39.194	38.572	39.783	39.183±0.605
5	46.929	47.184	46.692	46.935±0.246
6	58.127	57.189	57.742	57.684±0.474
7	62.685	62.138	63.716	62.846±0.801
8	67.184	68.125	68.915	68.074±0.866
9	73.857	72.447	73.124	73.142±0.705
10	79.544	80.192	79.722	79.819±0.348
11	87.195	86.334	86.192	86.573±0.542
12	93.915	94.752	94.138	94.268±0.433

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F4

Table no: 18

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	18.982	17.109	17.714	17.935±0.955
2	23.114	22.182	23.816	23.816±0.819
3	27.584	26.182	26.789	26.851±0.703
4	34.716	33.189	33.430	33.855±0.745
5	39.089	38.419	38.416	38.641±0.387
6	43.815	44.515	43.023	43.784±0.746
7	52.693	51.312	50.122	51.375±1.287
8	65.109	65.324	64.017	64.816±0.700
9	71.857	70.168	69.832	70.619±1.085
10	76.394	77.681	76.891	76.988±0.649
11	88.346	87.638	88.431	88.138±0.435
12	95.618	94.329	96.134	95.360±0.929

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F5

Table no :19

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	13.142	12.816	13.134	13.030±0.185
2	21.713	21.424	22.318	21.818±0.456
3	30.328	31.682	29.131	30.380±1.276
4	37.178	36.124	36.816	36.706±0.534
5	44.719	46.128	44.115	44.987±1.037
6	55.888	54.798	55.323	55.336±0.545
7	64.382	63.787	64.813	64.327±0.515
8	70.294	71.792	70.531	70.872±0.805
9	78.818	77.137	78.198	78.051±0.850
10	84.315	83.124	84.915	84.118±0.911
11	90.198	91.713	901.770	90.893±0.765
12	97.467	96.185	97.074	96.908±0.656

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F6

Table no: 20

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	22.348	21.889	21.033	21.756±0.667
2	30.176	29.701	29.215	29.697±0.480
3	35.219	34.138	35.713	35.023±0.805
4	40.184	39.632	39.141	39.652±0.521
5	44.515	44.815	43.134	44.154±0.896
6	47.817	48.127	47.124	47.713±0.473
7	57.693	58.613	59.543	58.616±0.925
8	69.715	68.185	69.008	68.969±0.765
9	76.138	75.714	75.983	75.945±0.214
10	83.650	84.365	83.218	83.744±0.579
11	90.127	91.423	89.809	90.453±0.855
12	96.532	96.654	95.340	96.175±0.726

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F7

Table no: 21

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	15.962	14.192	14.038	14.730±1.069
2	20.384	21.483	21.943	21.270±0.801
3	27.135	26.836	27.153	27.641±0.178
4	34.638	34.618	35.138	34.338±0.970
5	38.517	39.843	37.058	38.472±1.393
6	47.428	48.368	47.059	47.618±0.674
7	61.134	60.688	61.853	61.225±0.587
8	67.641	67.098	66.138	66.957±0.763
9	73.857	72.746	71.162	72.588±1.354
10	79.115	80.713	78.506	79.444±1.400
11	87.635	86.583	87.192	87.136±0.728
12	93.128	94.138	94.986	94.084±0.930

IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F8

Table no: 22

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	11.859	12.698	13.456	12.671±0.798
2	16.334	17.186	16.168	16.562±0.546
3	24.866	23.186	23.916	23.989±0.842
4	31.218	33.168	33.612	32.666±1.274
5	37.127	38.128	37.716	37.657±0.503
6	45.718	46.186	46.913	46.272±0.602
7	53.694	54.713	531.198	53.868±0.772
8	68.899	67.816	68.784	68.499±0.594
9	68.384	67.136	68.731	68.083±0.838
10	77.463	78.802	76.314	77.526±1.245
11	86.145	86.912	86.716	86.591±0.398
12	95.541	96.128	96.932	96.200±0.698

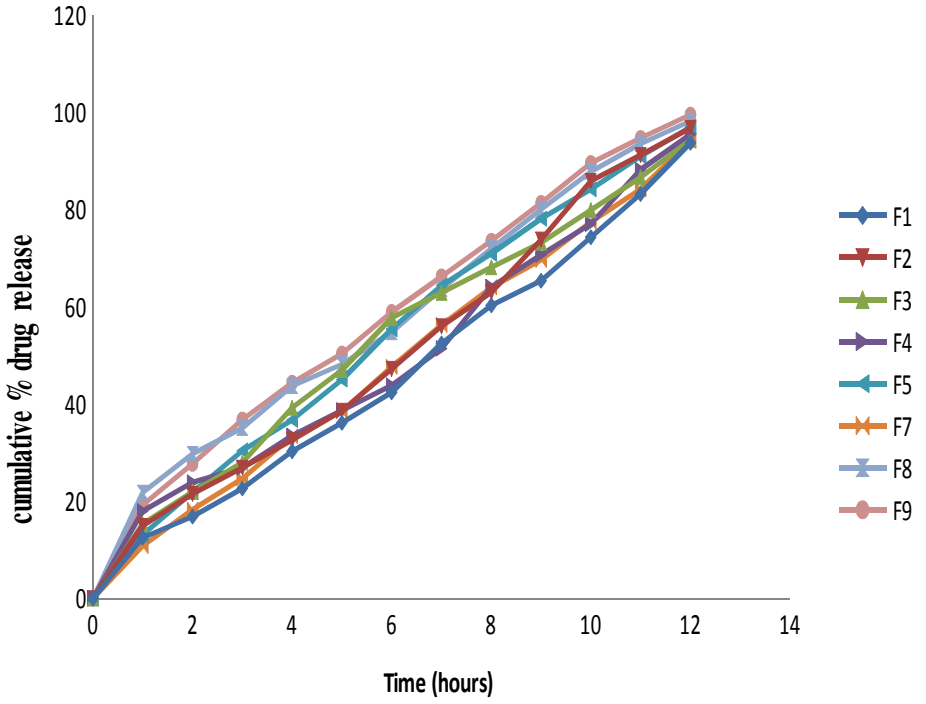
IN VITRO DRUG RELEASE PROFILE FOR FORMULATION F9

Table no: 23

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	14.584	14.139	15.720	14.814±0.815
2	21.658	20.716	22.189	21.530±0.758
3	27.343	26.716	26.217	26.758±0.564
4	34.832	33.192	34.917	34.313±0.972
5	39.465	40.128	41.762	40.451±1.182
6	47.763	48.716	47.185	47.888±0.773
7	56.078	55.862	56.632	56.190±0.397
8	65.957	65.444	64.504	65.301±0.736
9	73.562	74.710	75.313	74.528±0.887
10	82.809	83.404	81.312	82.508±1.078
11	92.811	90.113	92.213	91.712±1.417
12	98.645	97.632	96.503	97.593±1.072

CUMULATIVE PERCENTAGE DRUG RELEASE

Fig 11: comparative release profile of formulations F1 – F9



8.4 Kinetic values obtained from different plots of Formulations (F1– F9)

Table No: 24

F.code	Zero-order plots	First-order plots	Higuchi's Plots	Korsmeyer et al's plots		Possible Drug Release mechanism
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)	
F1	0.990	0.847	0.968	0.856	0.991	Zero order Fickian
F2	0.992	0.842	0.945	1.041	0.994	Zero order Fickian
F3	0.987	0.902	0.985	10.768	0.992	Zero order Fickian
F4	0.985	0.817	0.928	0.991	0.984	Zero order Fickian
F5	0.994	0.867	0.986	0.855	0.996	Zero order Non-fickian
F6	0.979	0.848	0.943	0.871	0.980	Zero order Non-fickian
F7	0.995	0.889	0.972	0.992	0.995	Zero order Non-fickian
F8	0.996	0.798	0.956	0.998	0.995	Zero order Non-fickian
F9	0.997	0.812	0.964	0.957	0.996	Zero order non-fickian

In vitro Dissolution Profile and Kinetic Plots of Formulation (F1)

Fig 12: Zero order Kinetic Plots of Formulation

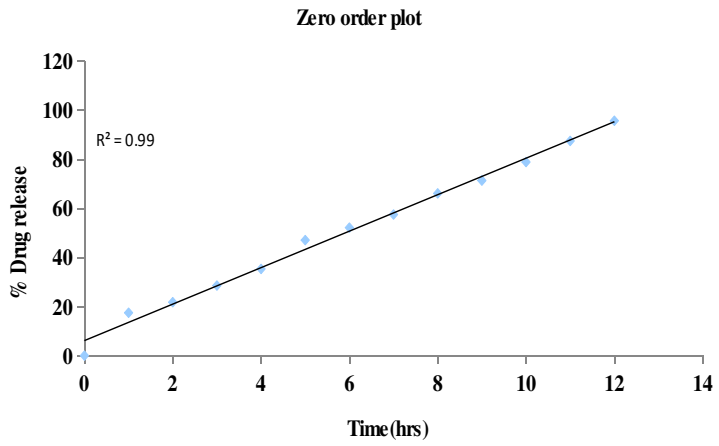


Fig 13: First order Kinetic Plots of Formulation

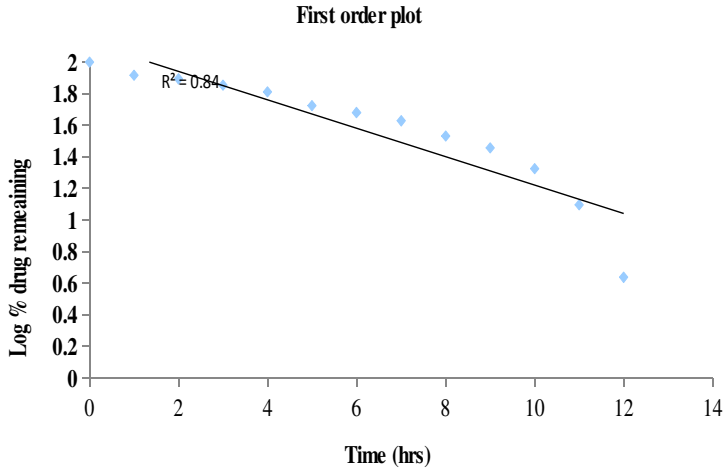


Fig 14: Korsmeyer Kinetic Plots of Formulation

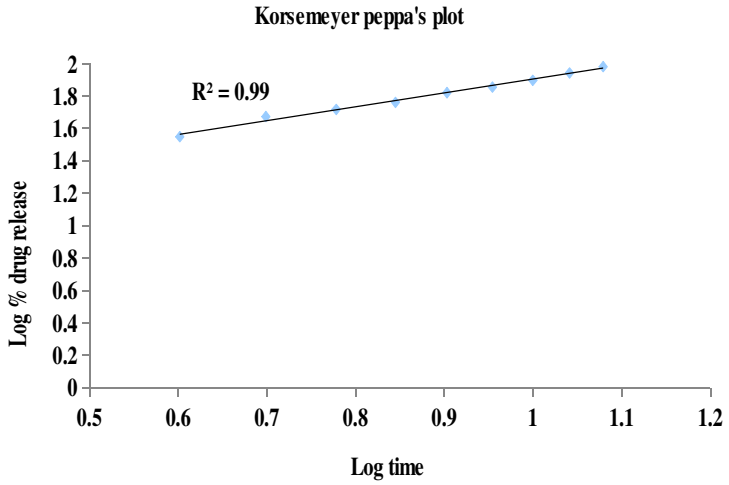
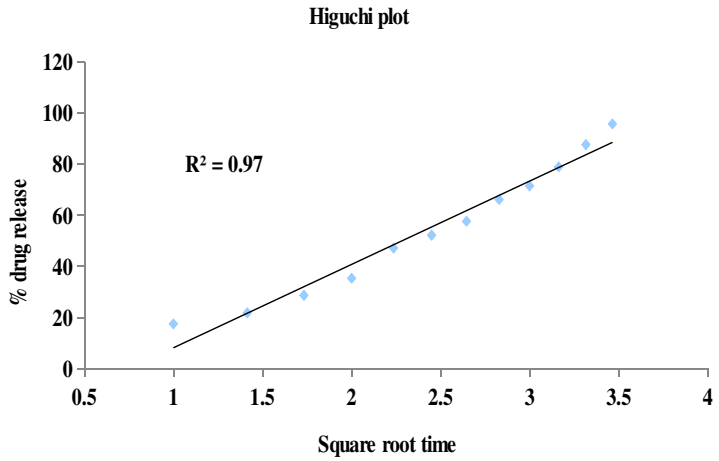


Fig 15: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F2)

Fig 16: Zero order Kinetic Plots of Formulation

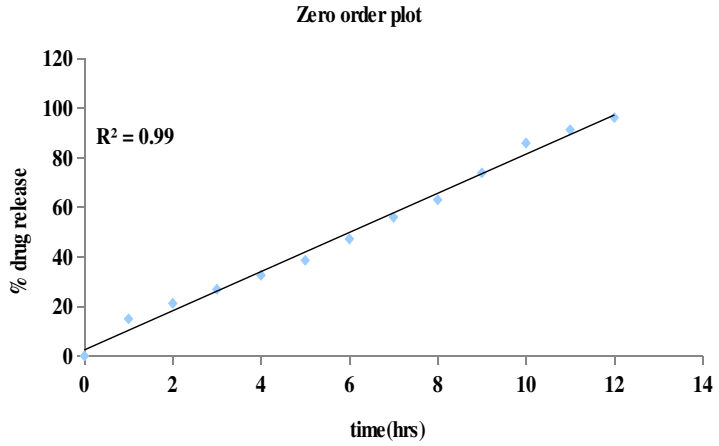


Fig 17: First order Kinetic Plots of Formulation

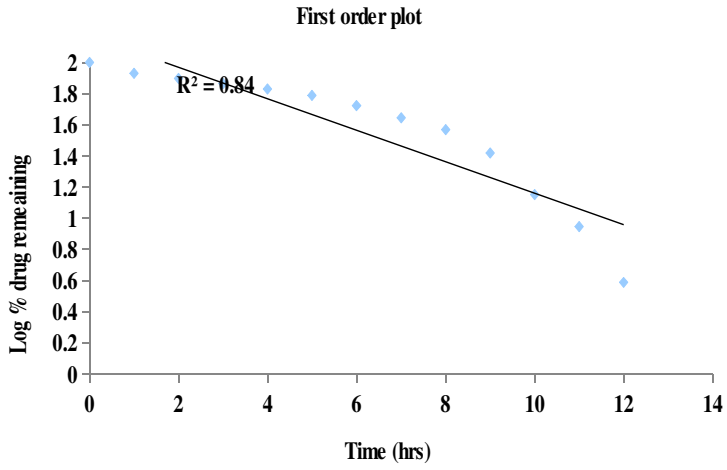


Fig 18: Korsmeyer Kinetic Plots of Formulation

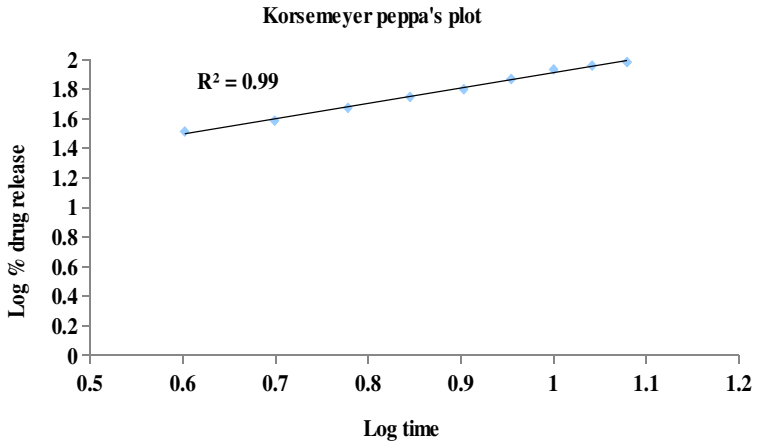
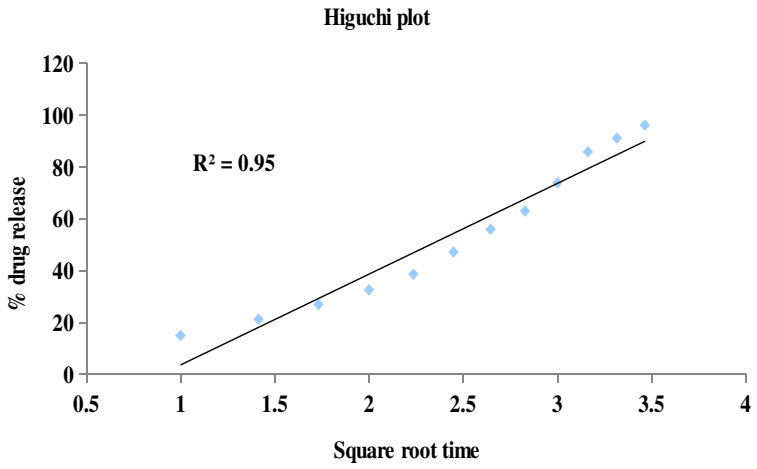


Fig 19: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F3)

Fig 20: Zero order Kinetic Plots of Formulation

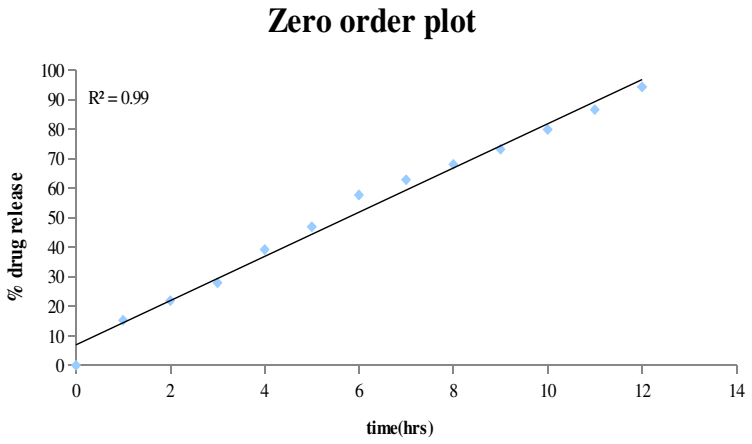


Fig 21s: First order Kinetic Plots of Formulation

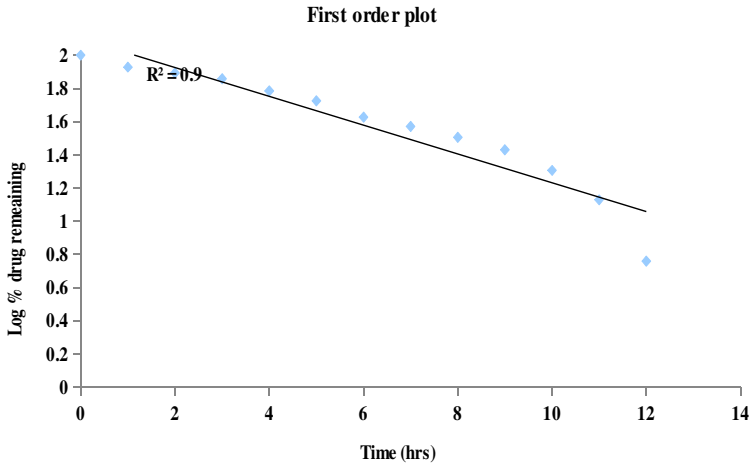


Fig 22: Korsmeyer Kinetic Plots of Formulation

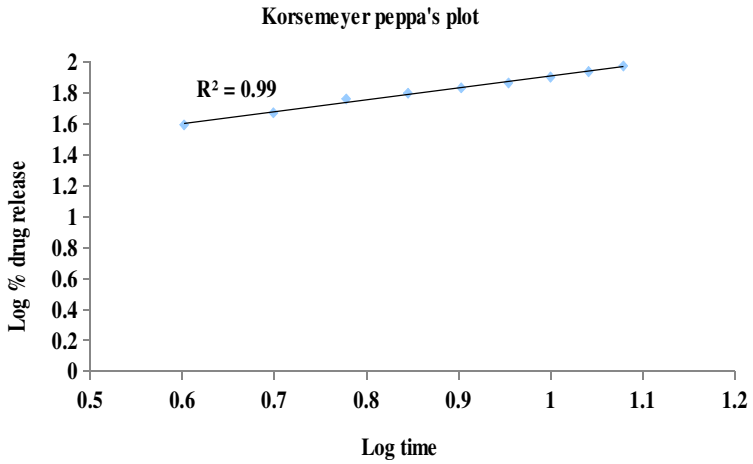
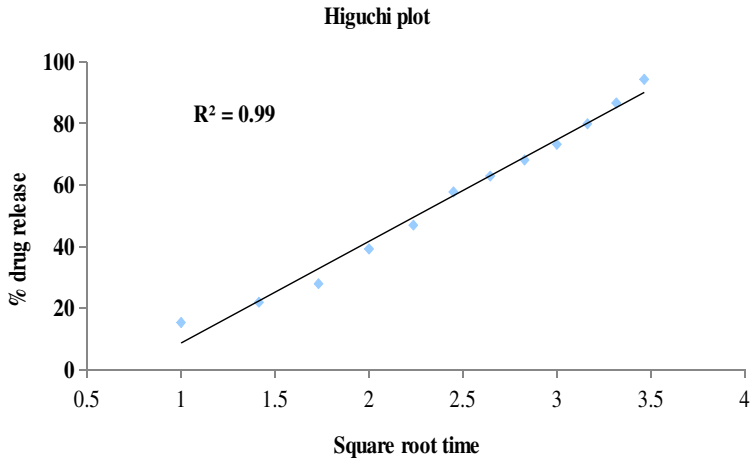


Fig 23: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F4)

Fig 24: Zero order Kinetic Plots of Formulation

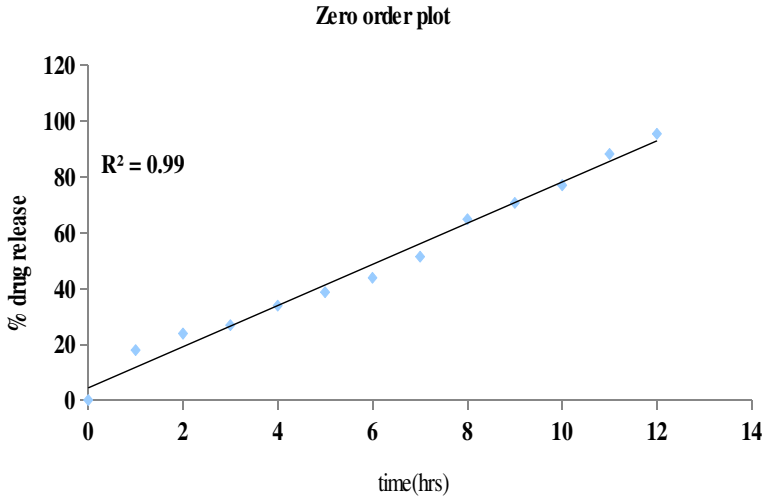


Fig 25: First order Kinetic Plots of Formulation

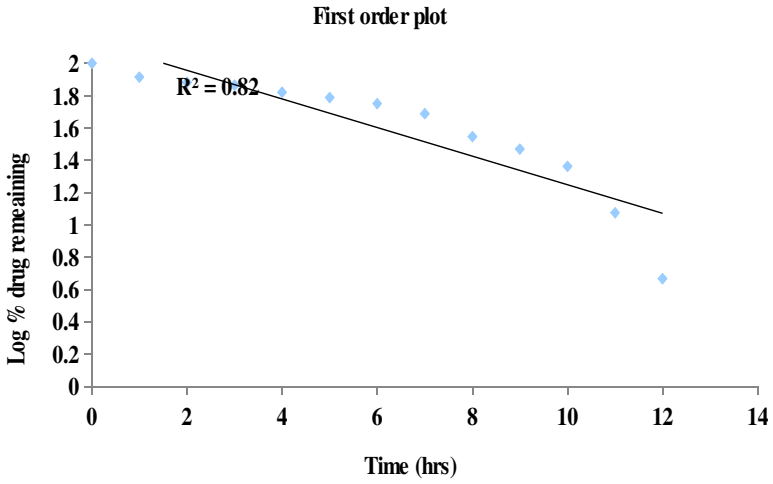


Fig 26: Korsmeyer Kinetic Plots of Formulation

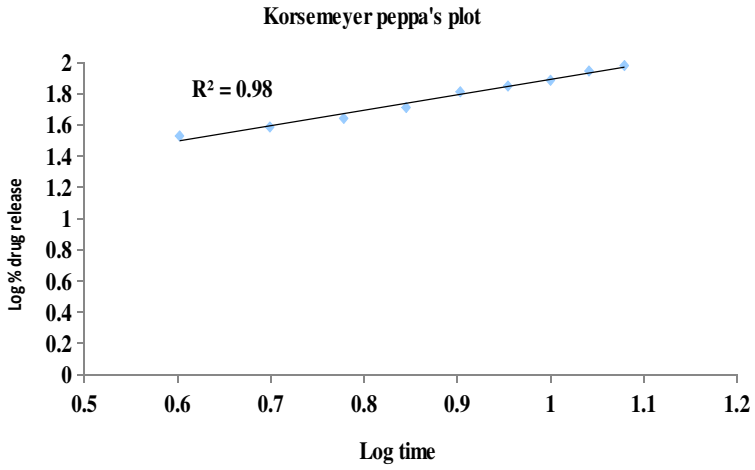
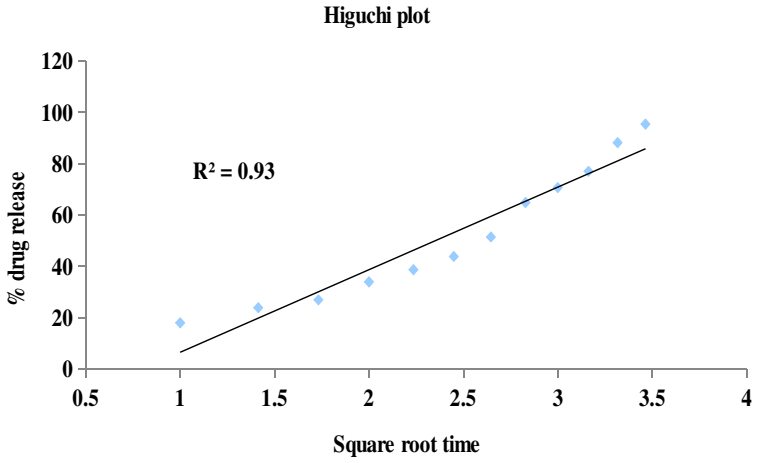


Fig 27: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F5)

Fig 28: Zero order Kinetic Plots of Formulation

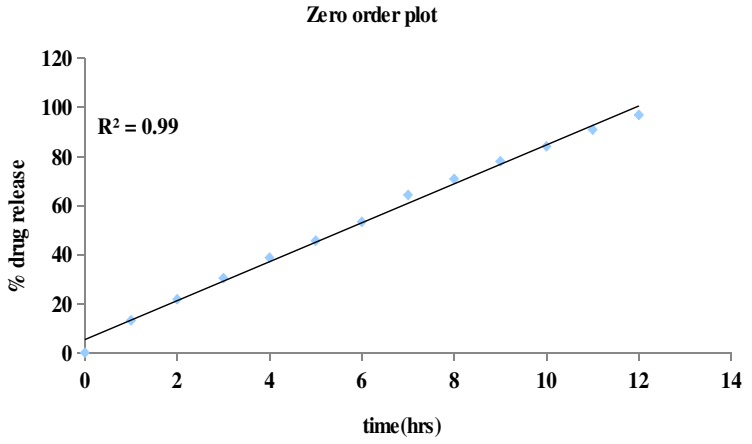


Fig 29: First order Kinetic Plots of Formulation

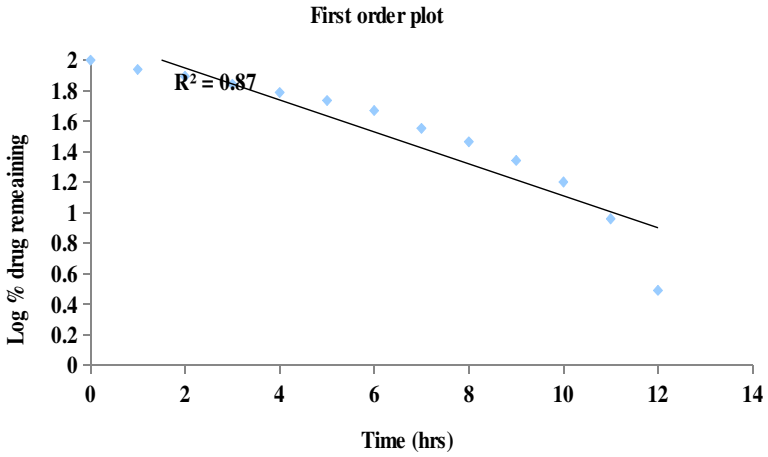


Fig 30: Korsmeyer Kinetic Plots of Formulation

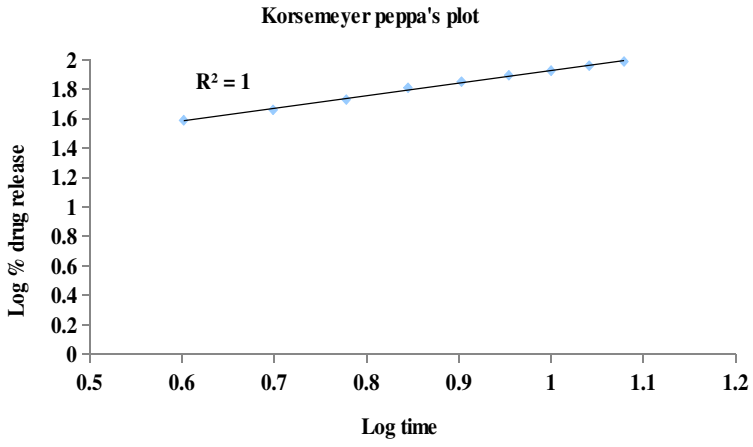
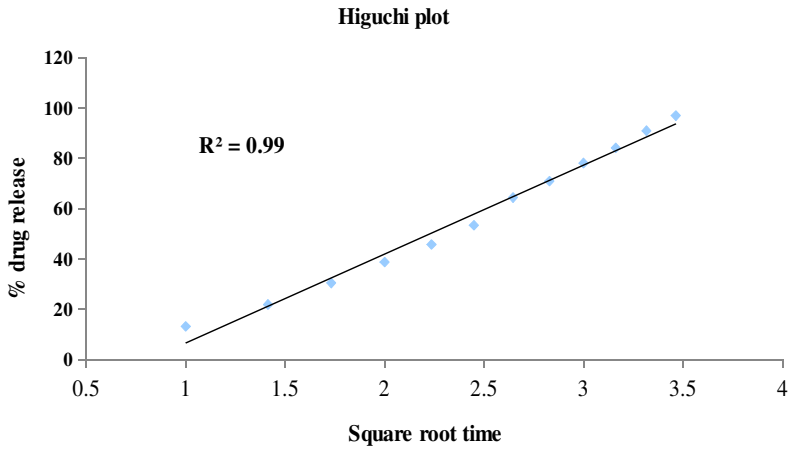


Fig 31: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F6)

Fig 32: Zero order Kinetic Plots of Formulation

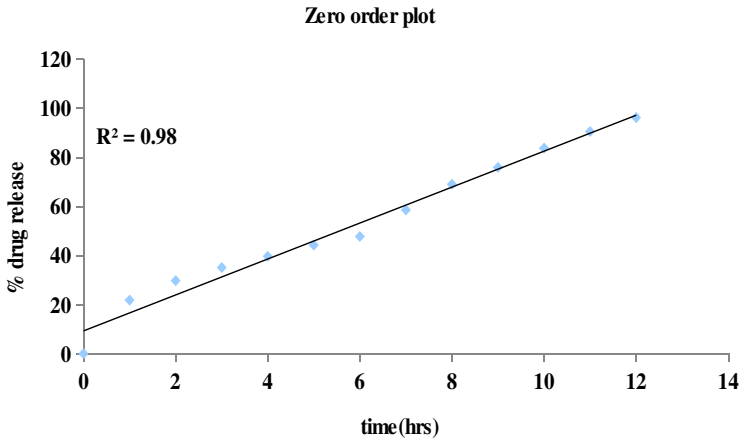


Fig 33: First order Kinetic Plots of Formulation

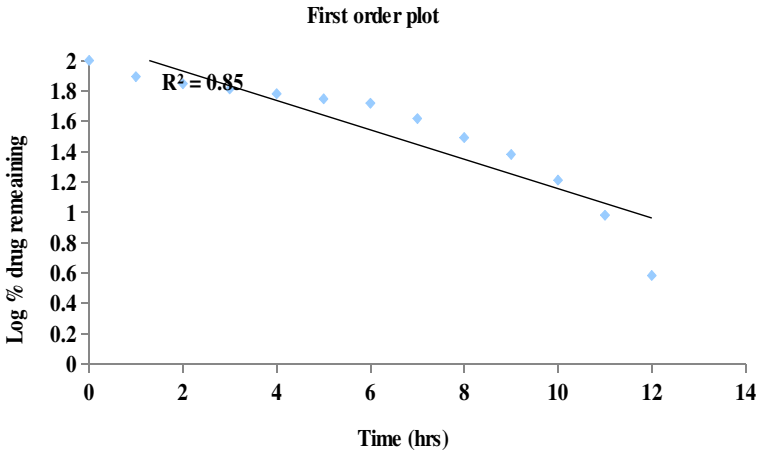


Fig 34: Korsmeyer Kinetic Plots of Formulation

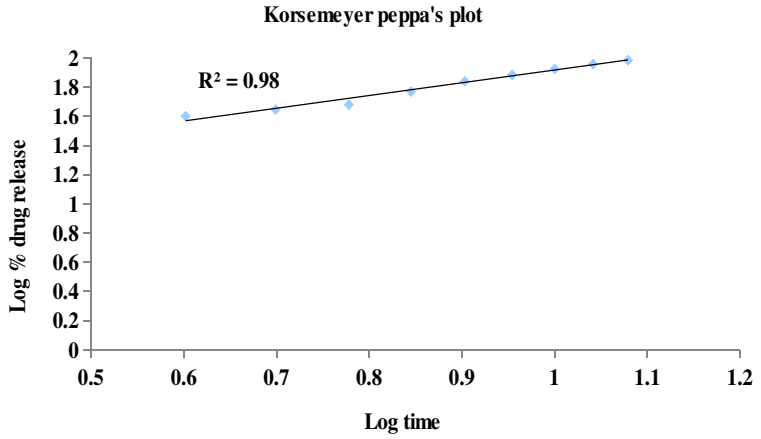
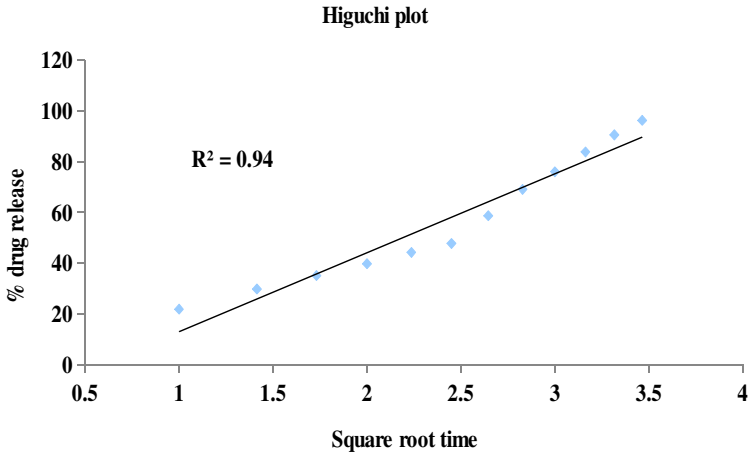


Fig 35: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F7)

Fig 36: Zero order Kinetic Plots of Formulation

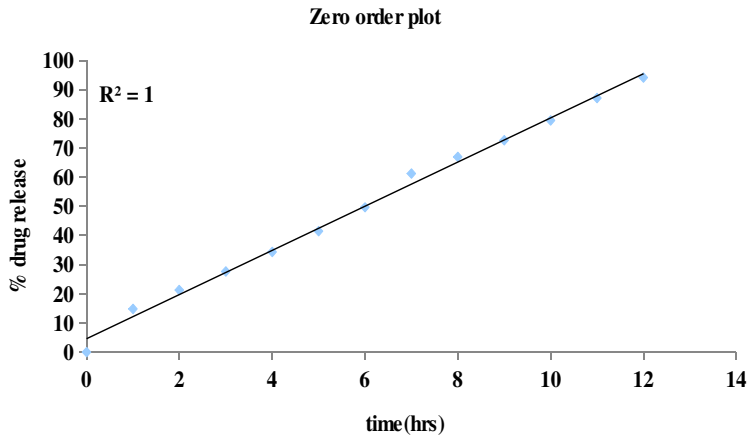


Fig 37: First order Kinetic Plots of Formulation

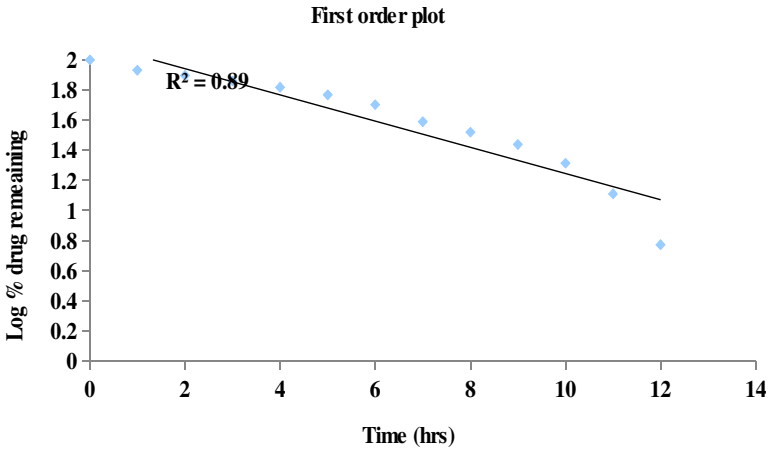


Fig 38: Korsmeyer Kinetic Plots of Formulation

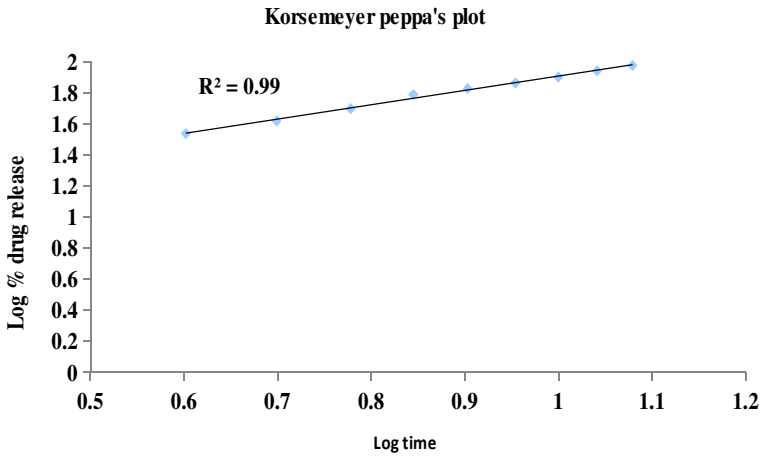
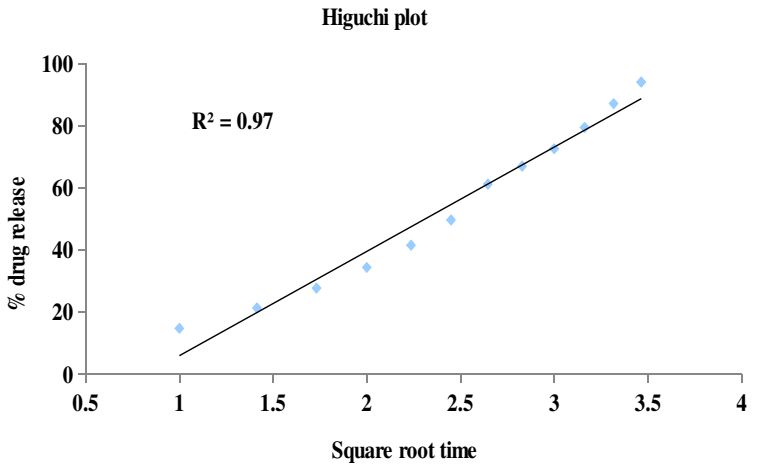


Fig 39: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F8)

Fig 40: Zero order Kinetic Plots of Formulation

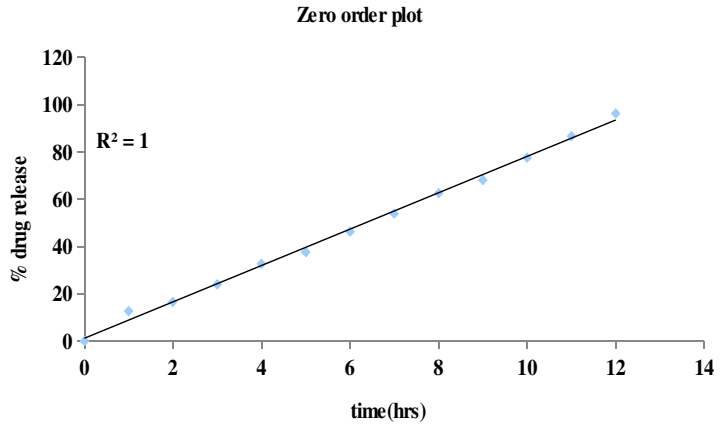


Fig 41: First order Kinetic Plots of Formulation

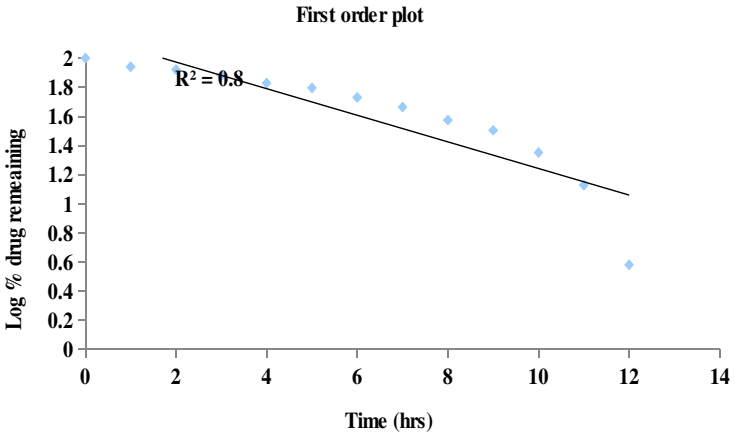


Fig 42: Korsmeyer Kinetic Plots of Formulation

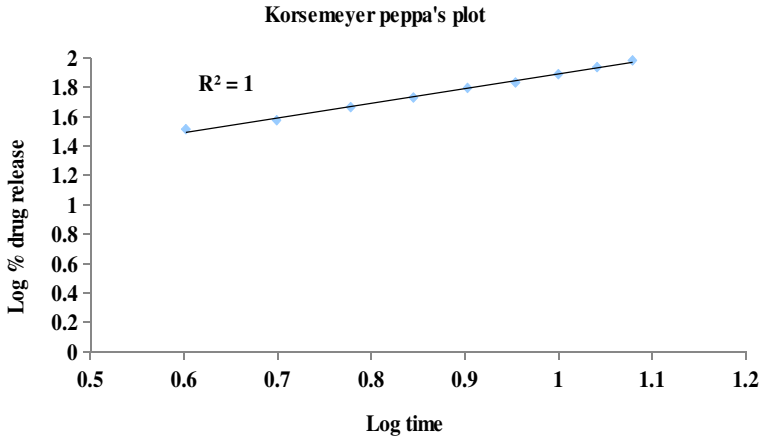
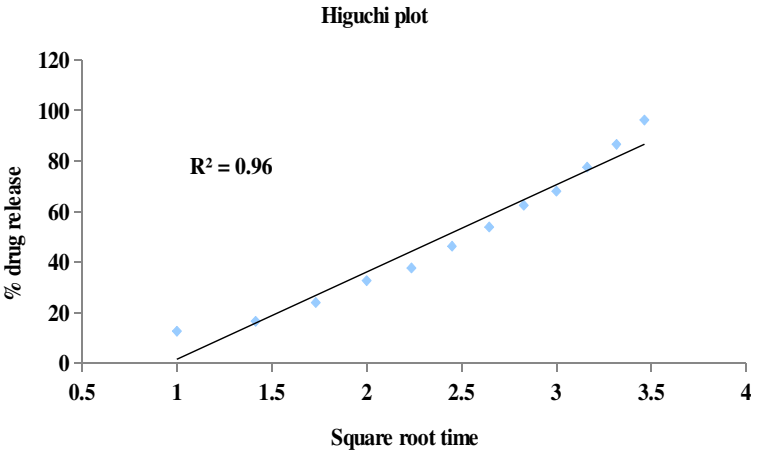


Fig 43: Higuichi's Kinetic Plots of Formulation



In vitro Dissolution Profile and Kinetic Plots of Formulation (F9)

Fig 44: Zero order Kinetic Plots of Formulation

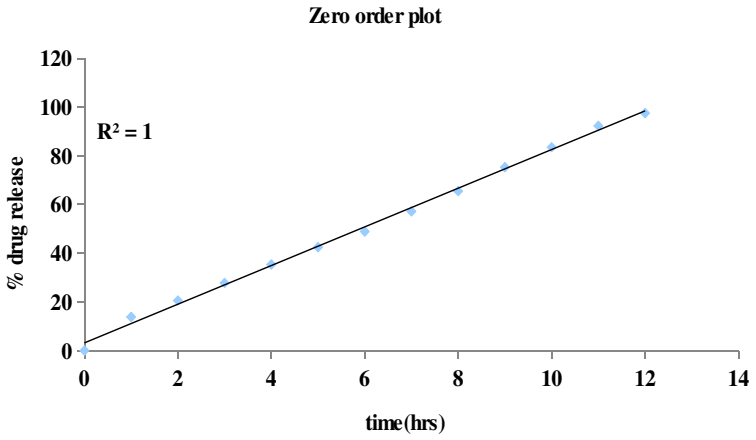


Fig 45: First order Kinetic Plots of Formulation

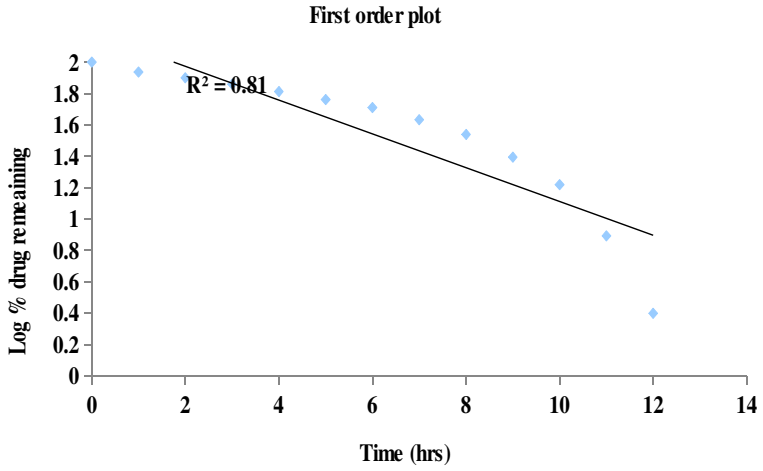


Fig 46: Korsmeyer Kinetic Plots of Formulation

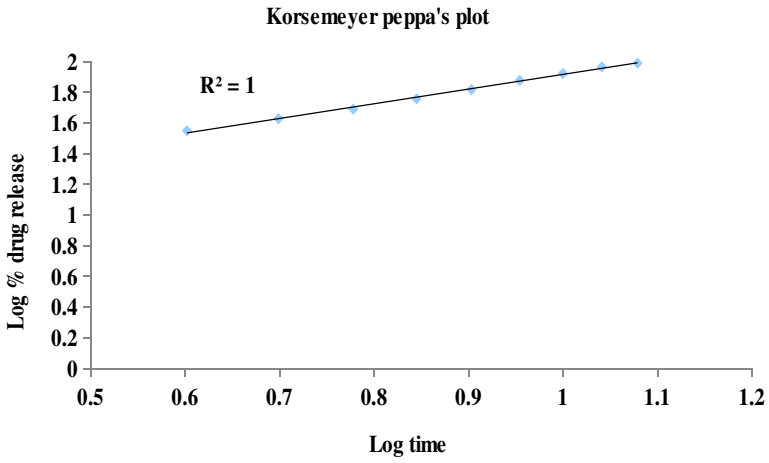
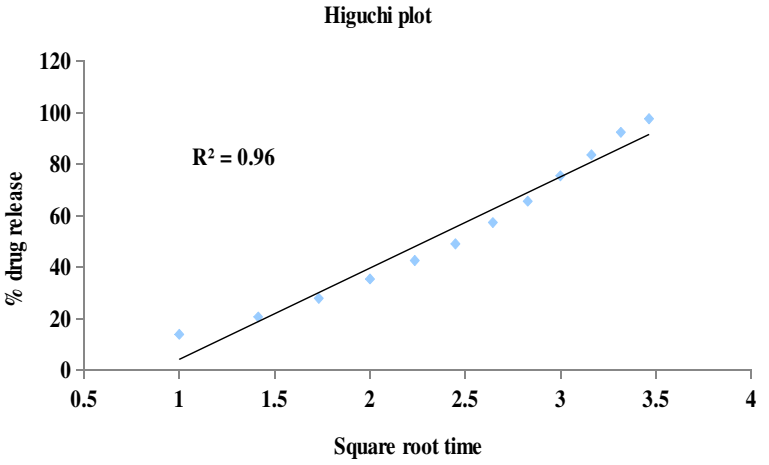


Fig 47: Higuichi's Kinetic Plots of Formulation



8.6 EX VIVO DRUG PERMEATION FOR FORMULATION

All the nine formulations of prepared mucoadhesive buccal tablets of atorvastatin calcium were subjected to ex vivo permeation studies were carried out by using Franz diffusion cell. The values were tabulated in the following tables.

EX VIVO DRUG PERMEATION FOR FORMULATION F1

Table no 24

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	2.954	3.110	2.990	3.017±0.0828
2	7.354	7.575	7.781	7.570±0.213
3	12.210	11.803	12.121	12.044±0.214
4	19.321	19.991	19.500	19.604±0.346
5	26.718	26.937	27.101	26.918±0.192
6	34.890	34.751	34.230	34.623±0.347
7	42.387	42.110	41.989	42.162±0.204
8	45.988	44.113	44.221	44.107±0.116
9	51.816	51.550	51.982	51.782±0.217
10	59.210	58.991	58.880	59.027±0.167
11	67.586	67.238	67.690	67.504±0.236
12	75.801	75.210	75.394	75.468±0.302

EX VIVO PERMEATION FOR FORMULATION F2

Table no 25

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	7.982	7.310	8.104	7.798±0.427
2	12.298	12.353	11.991	12.214±0.195
3	16.898	17.121	16.985	16.991±0.115
4	22.817	22.534	22.237	22.529±0.290
5	28.976	29.219	28.898	29.128±0.334
6	35.821	35.690	36.100	35.870±0.209
7	43.894	43.234	43.983	43.703±0.409
8	51.970	52.210	52.319	52.166±0.178
9	60.129	60.713	59.897	60.246±0.420
10	67.810	67.343	68.137	67.763±0.399
11	72.584	72.373	72.981	72.312±0.306
12	77.991	77.404	77.151	77.848±0.393

EX VIVO DRUG PERMEATION FOR FORMULATION F3

Table no 26

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	7.389	6.890	6.690	6.989±0.360
2	11.121	11.314	10.881	11.105±0.216
3	17.890	18.134	17.534	17.852±0.301
4	23.210	23.811	22.901	23.307±0.462
5	30.568	31.217	30.896	30.893±0.324
6	35.996	36.324	36.585	36.301±0.295
7	42.312	41.889	42.529	42.243±0.325
8	51.812	52.234	51.594	51.880±0.325
9	58.816	59.213	59.325	59.051±0.208
10	67.713	68.211	67.934	67.952±0.249
11	76.312	76.690	75.861	76.287±0.415
12	84.410	85.128	84.816	84.784±0.360

BATCH II

EX VIVO DRUG PERMEATION FOR FORMULATION F4

Table no 27

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	10.221	9.850	10.214	10.095±0.212
2	14.213	13.710	14.580	14.127±0.436
3	18.410	18.213	19.381	18.668±0.625
4	23.160	23.675	22.750	23.197±0.460
5	31.890	31.217	32.318	31.808±0.555
6	37.515	38.308	37.121	37.648±0.604
7	43.897	44.412	43.785	44.031±0.334
8	53.116	53.855	52.779	53.250±0.550
9	60.413	60.890	61.412	60.905±0.499
10	69.235	69.990	68.185	69.136±0.906
11	77.121	76.667	77.685	77.157±0.510
12	86.584	85.764	86.125	86.157±0.411

BATCH II

EX VIVO DRUG PERMEATION FOR FORMULATION F5

Table no 28

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	6.985	5.997	6.385	6.455±0.497
2	10.584	11.313	10.213	10.703±0.559
3	16.813	16.213	17.318	16.781±0.553
4	23.185	23.681	22.891	23.254±0.402
5	29.135	28.890	29.524	29.183±0.319
6	36.813	37.185	35.994	36.664±0.609
7	44.185	44.767	44.585	45.179±0.591
8	53.125	53.885	52.482	53.164±0.702
9	58.361	58.817	59.212	58.796±0.425
10	68.861	68.217	67.719	68.265±0.572
11	77.121	77.818	76.836	77.258±0.505
12	84.589	85.301	84.761	83.883±0.371

BATCH II

EX VIVO DRUG PERMEATION FOR FORMULATION F6

Table no 29

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	4.954	4.321	5.224	4.833±0.463
2	9.876	9.420	8.886	9.394±0.495
3	16.803	15.986	16.349	16.379±0.409
4	22.845	23.185	23.585	23.205±0.370
5	30.312	30.916	31.181	30.803±0.445
6	36.618	37.321	36.513	36.513±0.439
7	43.976	42.524	43.124	43.208±0.729
8	49.432	49.916	50.525	49.957±0.547
9	55.581	56.918	55.997	56.165±0.684
10	66.301	66.716	66.519	67.178±0.607
11	74.481	74.892	73.756	74.76±0.575
12	83.321	83.990	82.627	83.312±0.681

BATCH III

EX VIVO DRUG PERMEATION FOR FORMULATION F7

Table no 30

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	5.320	5.918	5.133	5.457±0.409
2	10.231	11.432	10.872	10.845±0.601
3	17.868	18.324	18.525	18.172±0.331
4	23.485	24.915	24.215	24.205±0.715
5	31.586	30.315	30.915	30.938±0.635
6	37.425	37.608	37.918	37.650±0.249
7	42.781	43.623	43.925	43.443±0.592
8	52.325	51.353	51.915	51.197±0.788
9	59.723	60.399	59.232	59.784±0.585
10	67.896	68.282	67.434	67.870±0.424
11	77.383	77.913	76.219	77.171±0.866
12	84.404	85.905	86.672	85.993±0.800

EX VIVO DRUG PERMEATION FOR FORMULATION F8

Table no 31

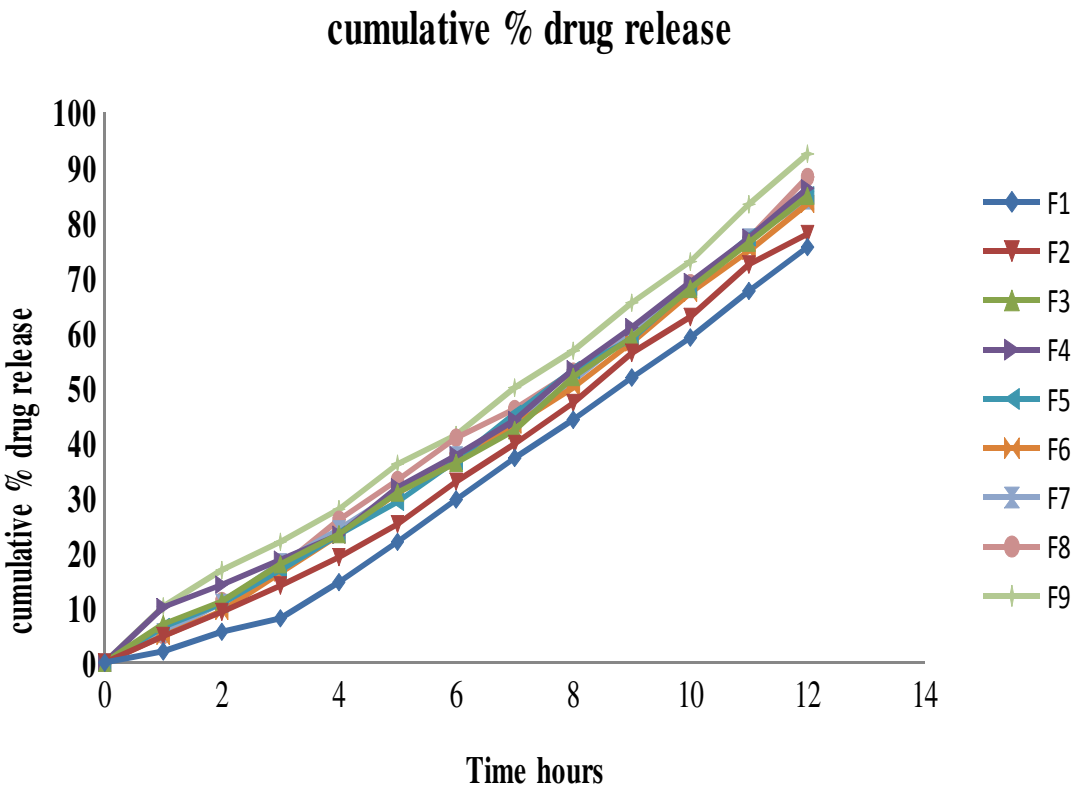
Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	2.958	3.816	2.125	2.966±0.845
2	8.147	8.581	7.769	8.165±0.406
3	13.983	14.481	14.394	14.286±0.266
4	20.618	21.327	20.882	20.942±0.358
5	28.121	28.890	27.425	28.145±0.732
6	35.381	36.613	35.525	35.839±0.673
7	42.761	43.481	42.863	43.035±0.389
8	50.301	51.311	50.863	50.825±0.506
9	57.289	58.115	57.896	57.766±0.427
10	65.815	66.537	65.389	65.913±0.580
11	75.904	75.224	74.898	74.008±0.842
12	84.543	83.325	84.743	84.203±0.767

EX VIVO DRUG PERMEATION FOR FORMULATION F9

Table no 32

Time (hrs)	Cumulative % of Drug Release			Mean ±SD
	1	2	3	
0	0	0	0	0
1	9.701	8.632	9.215	9.182±0.535
2	13.850	14.115	13.382	13.782±0.371
3	16.421	16.885	17.471	16.916±0.527
4	22.310	23.440	22.798	22.839±0.568
5	30.706	31.412	31.116	31.078±0.354
6	36.930	35.622	36.512	36.354±0.668
7	42.432	43.527	42.815	42.924±0.555
8	49.552	50.244	49.146	49.647±0.555
9	57.681	58.486	58.919	58.361±0.626
10	68.343	69.432	68.717	68.830±0.553
11	78.935	77.116	78.629	78.226±0.974
12	91.936	92.892	92.425	92.417±0.478

Fig 48:



8.5 Kinetic values obtained from different plots of Formulations (F1– F9)

Table - 33

F.code	Zero-order plots	First-order plots	Higuchi's Plots	Korsmeyer et al's plots		Possible Drug Release mechanism
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)	
F1	0.988	0.890	0.946	1.339	0.999	Zero order Fickian
F2	0.990	0.894	0.938	1.225	0.999	Zero order Fickian
F3	0.992	0.896	0.945	1.172	0.997	Zero order Fickian
F4	0.991	0.890	0.936	1.174	0.996	Zero order Fickian
F5	0.993	0.901	0.949	1.194	0.998	Zero order Non-fickian
F6	0.994	0.909	0.957	1.151	0.998	Zero order Non-fickian
F7	0.995	0.908	0.956	1.141	0.998	Zero order Non-fickian
F8	0.993	0.909	0.958	1.239	0.999	Zero order Non-fickian
F9	0.985	0.859	0.923	1.200	0.994	Zero order non-fickian

Ex vivo release Profile and Kinetic Plots of Formulation (F1)

Fig 49: Zero order Kinetic Plots of Formulation

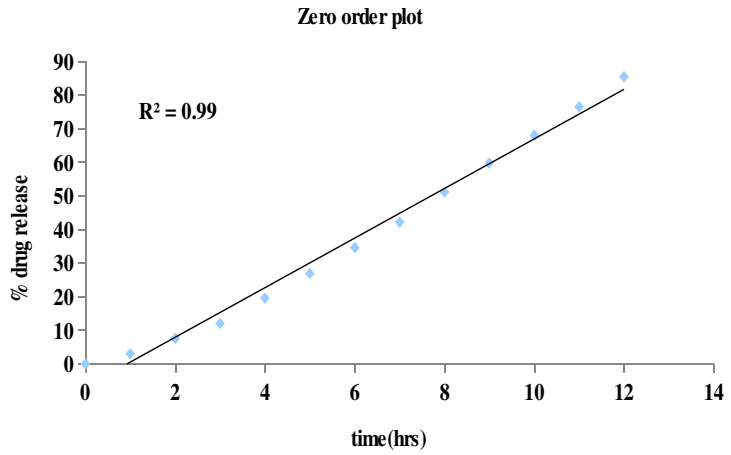


Fig 50: First order Kinetic Plots of Formulation

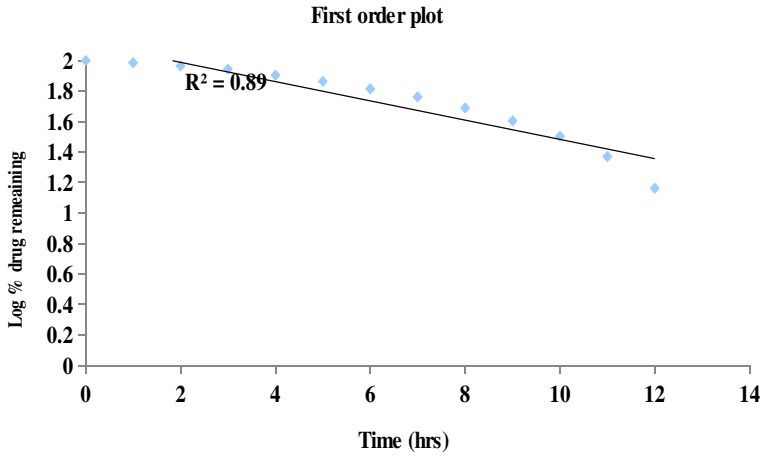


Fig 51: Korsmeyer Kinetic Plots of Formulation

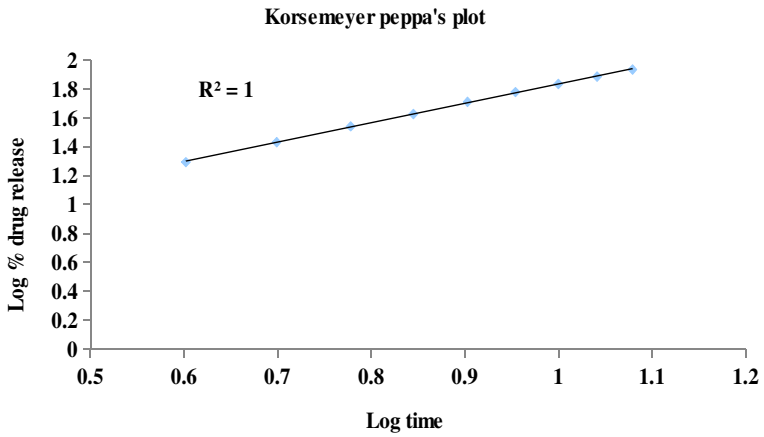
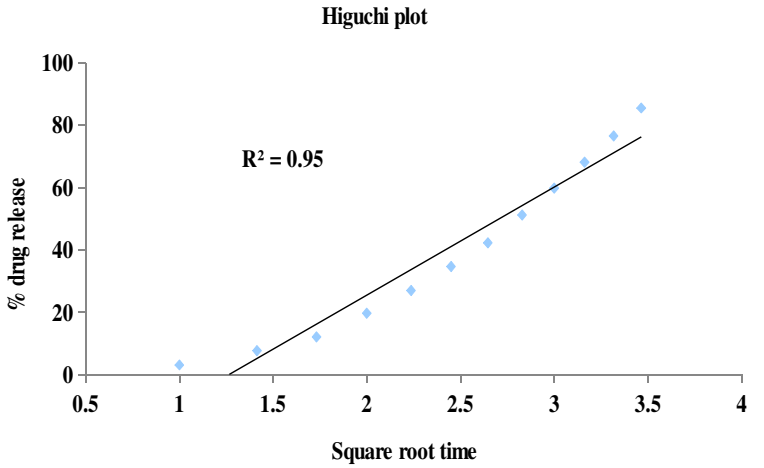


Fig 52: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F2)

Fig 53: Zero order Kinetic Plots of Formulation

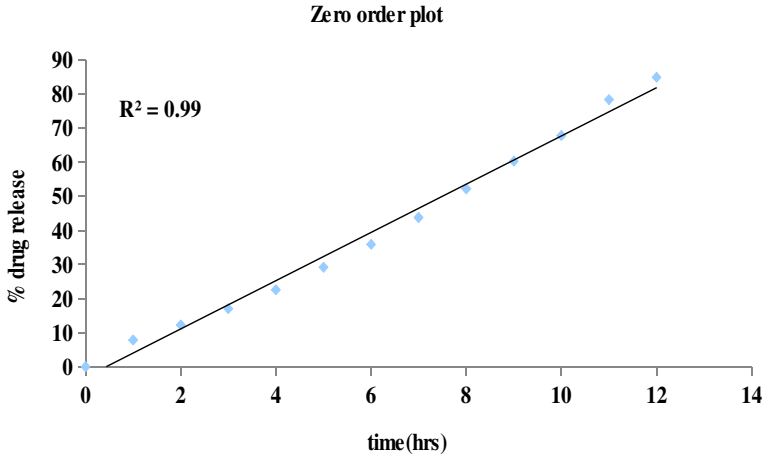


Fig 54: First order Kinetic Plots of Formulation

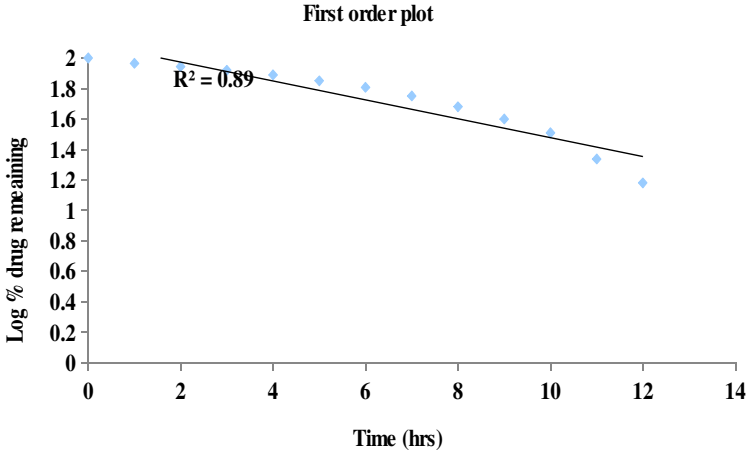


Fig 55: Korsmeyer Kinetic Plots of Formulation

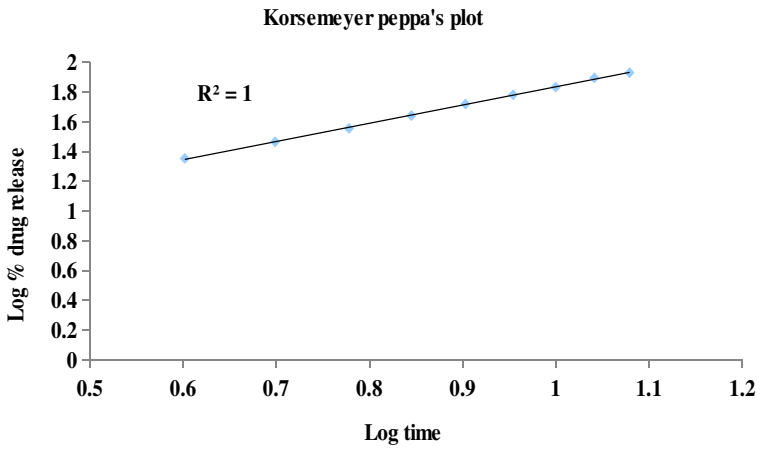
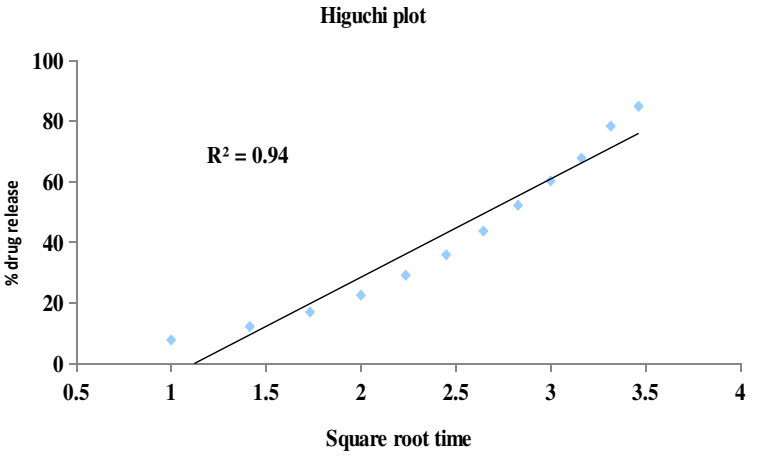


Fig 56: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F3)

Fig 57: Zero order Kinetic Plots of Formulation

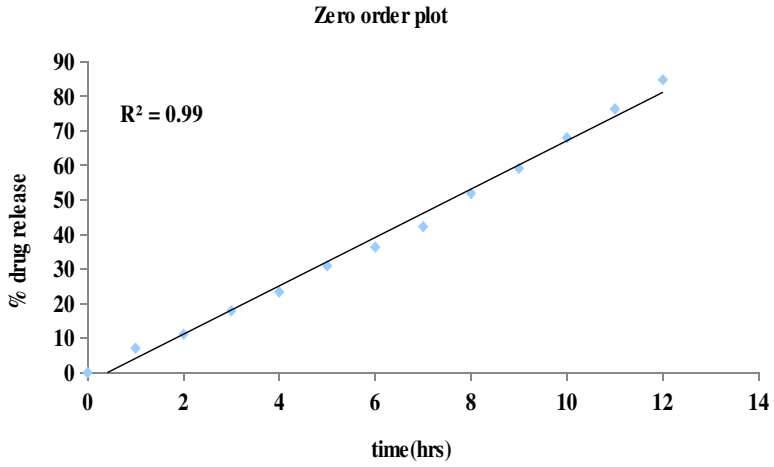


Fig 58: First order Kinetic Plots of Formulation

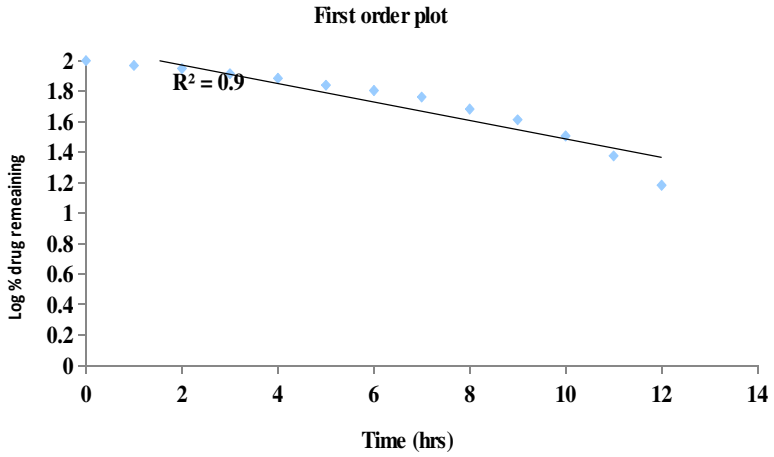


Fig 59: Korsmeyer Kinetic Plots of Formulation

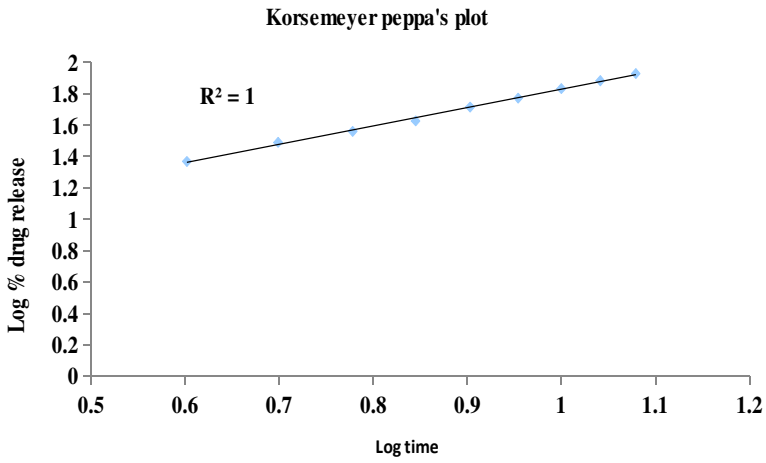
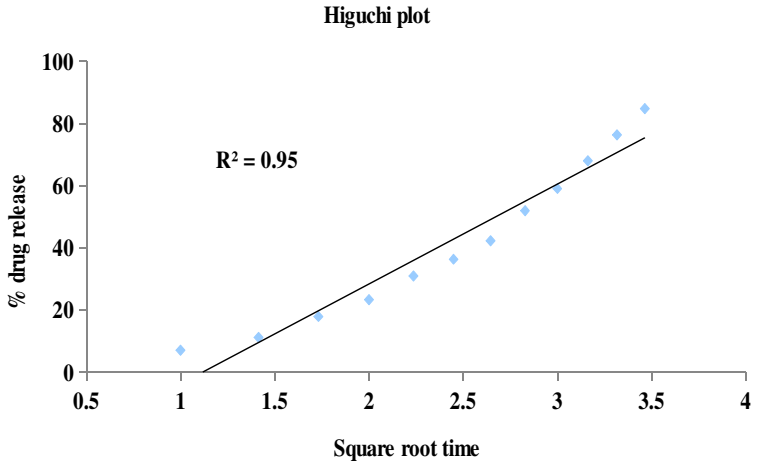


Fig 60: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F4)

Fig 61: Zero order Kinetic Plots of Formulation

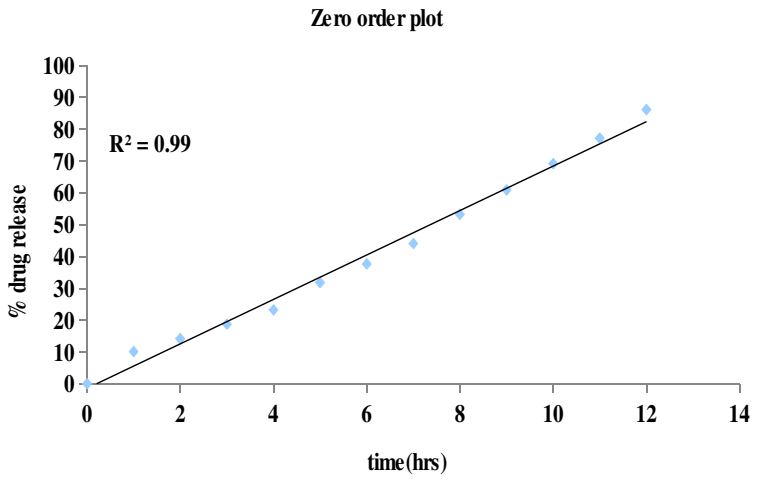


Fig 62: First order Kinetic Plots of Formulation

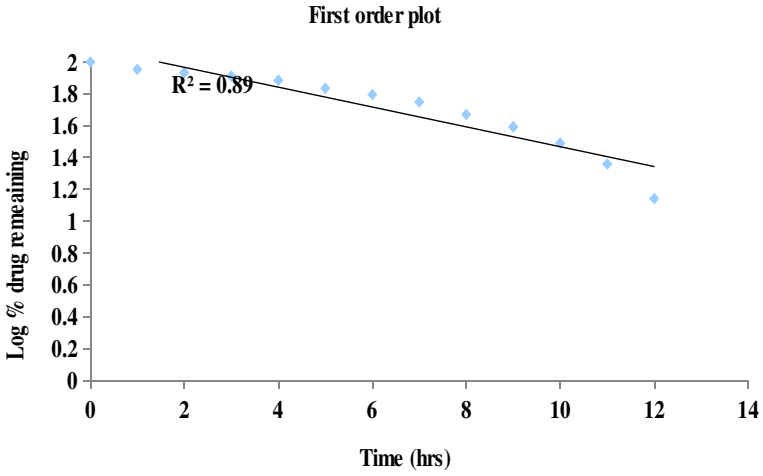


Fig 63: Korsmeyer Kinetic Plots of Formulation

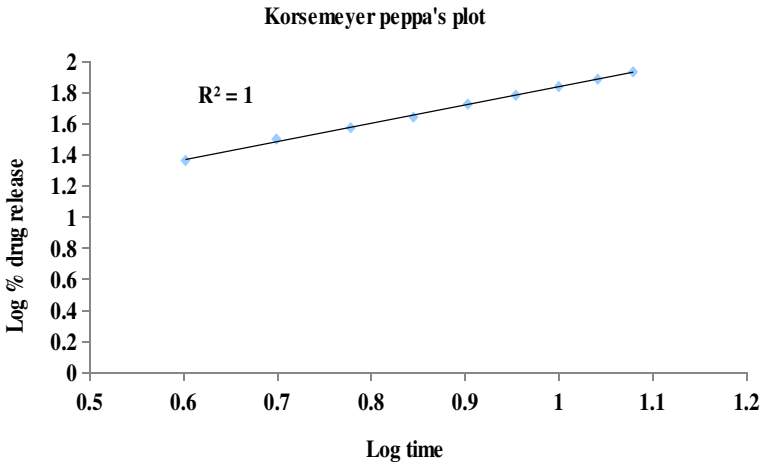
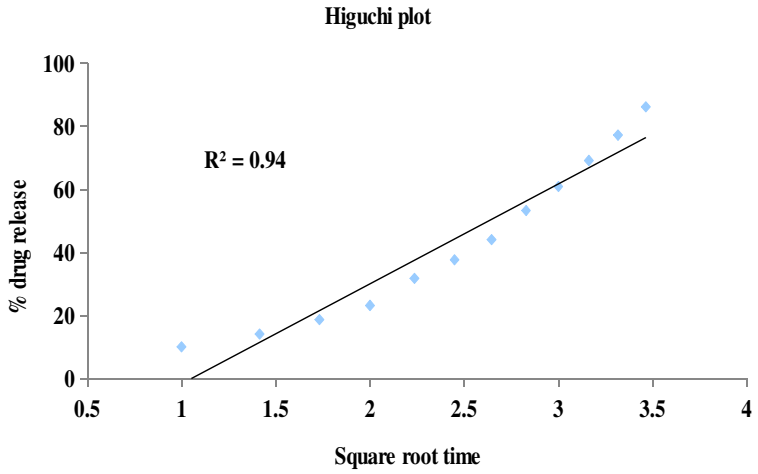


Fig 64: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F5)

Fig 65: Zero order Kinetic Plots of Formulation

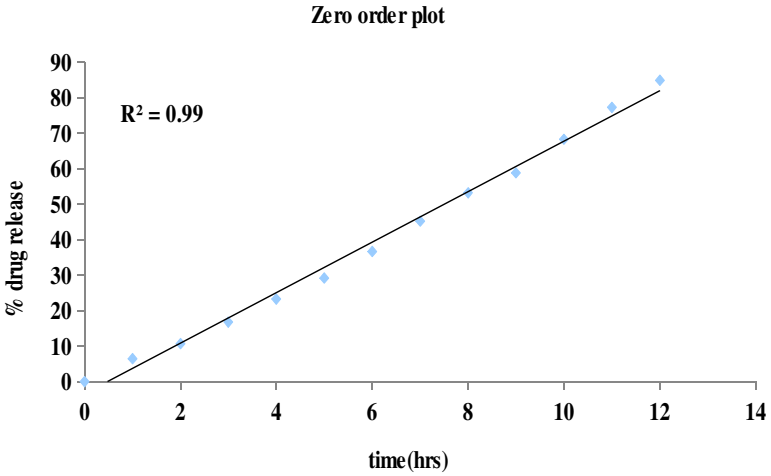


Fig 66: First order Kinetic Plots of Formulation

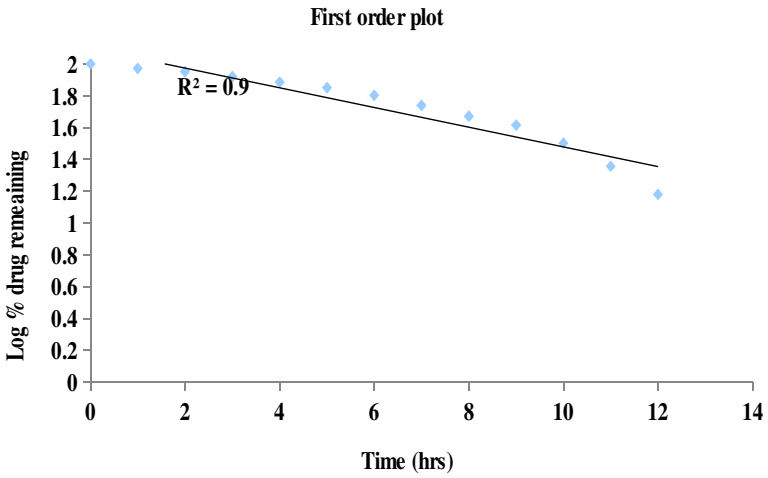


Fig 67: Korsmeyer Kinetic Plots of Formulation

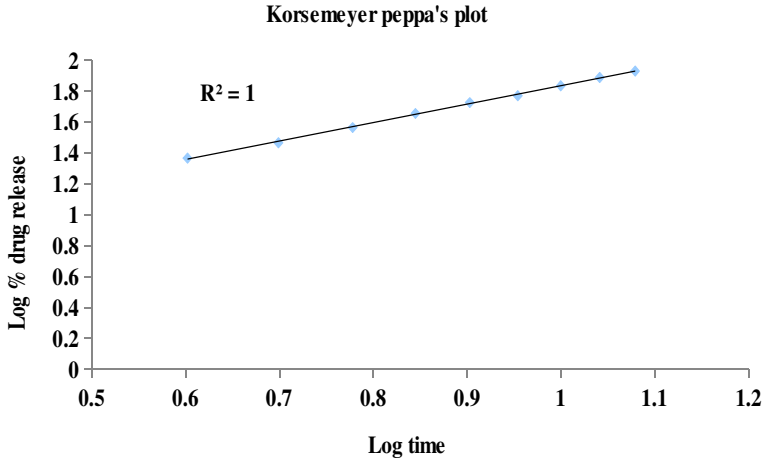
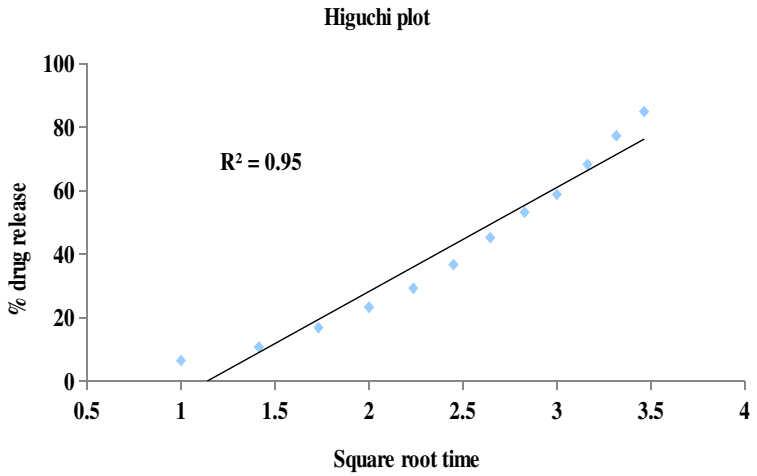


Fig 68: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F6)

Fig 69: Zero order Kinetic Plots of Formulation

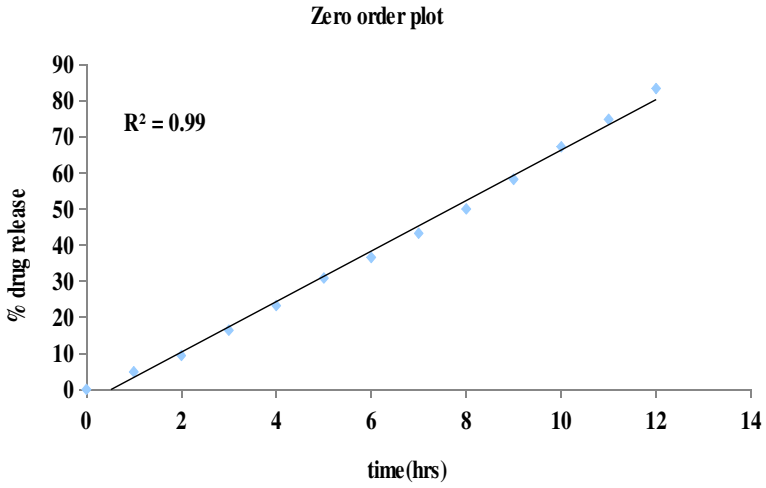


Fig 70: First order Kinetic Plots of Formulation

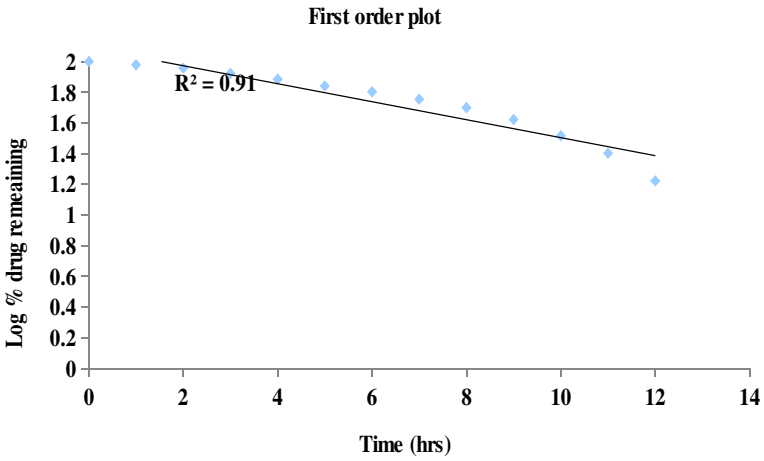


Fig 71: Korsmeyer Kinetic Plots of Formulation

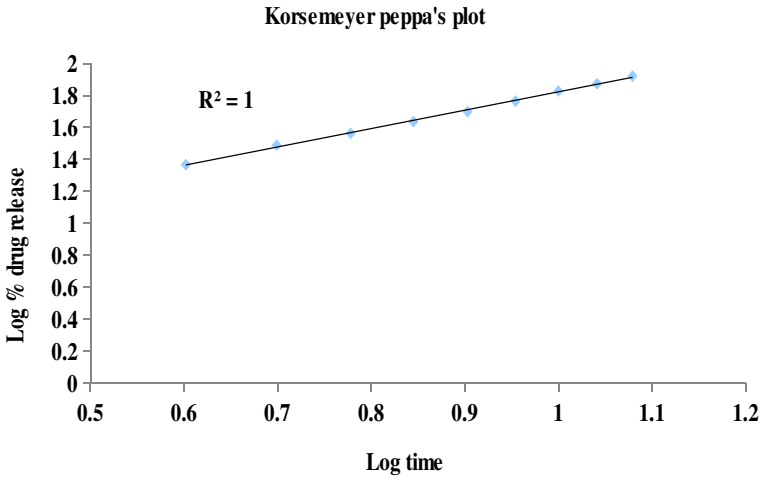
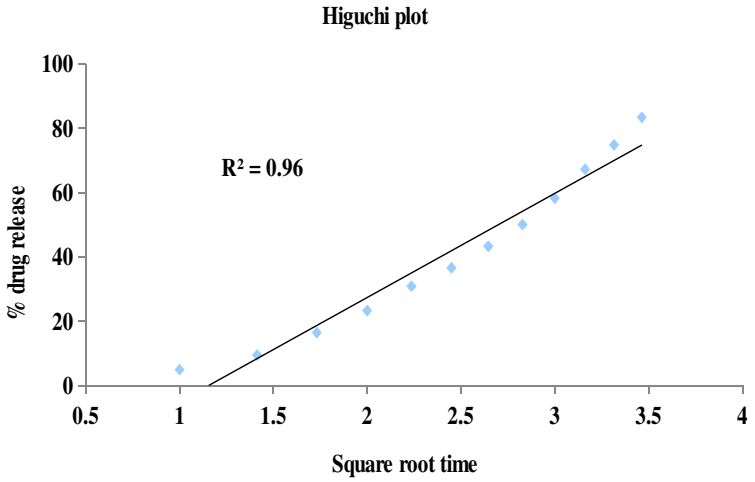


Fig 72: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F7)

Fig 73: Zero order Kinetic Plots of Formulation

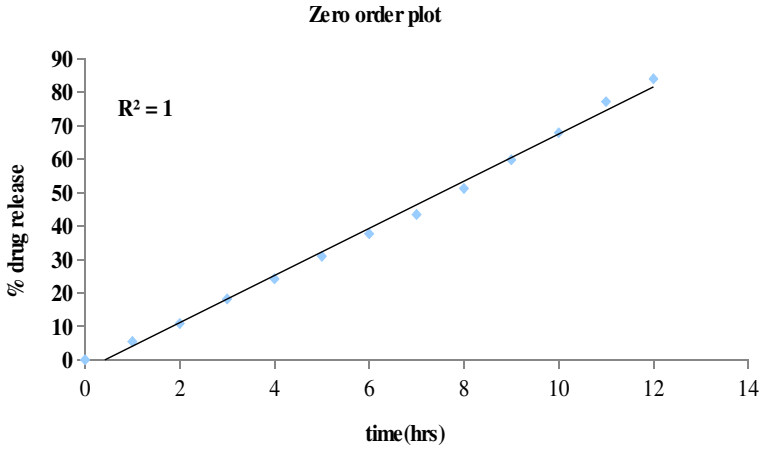


Fig 74: First order Kinetic Plots of Formulation

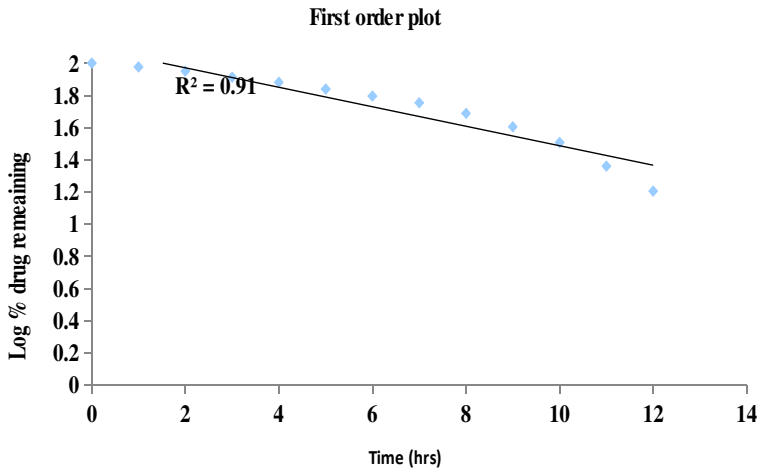


Fig 75: Korsmeyer Kinetic Plots of Formulation

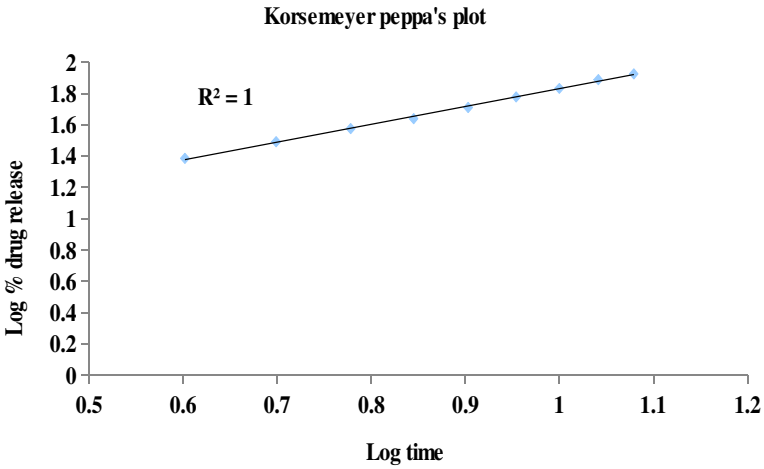
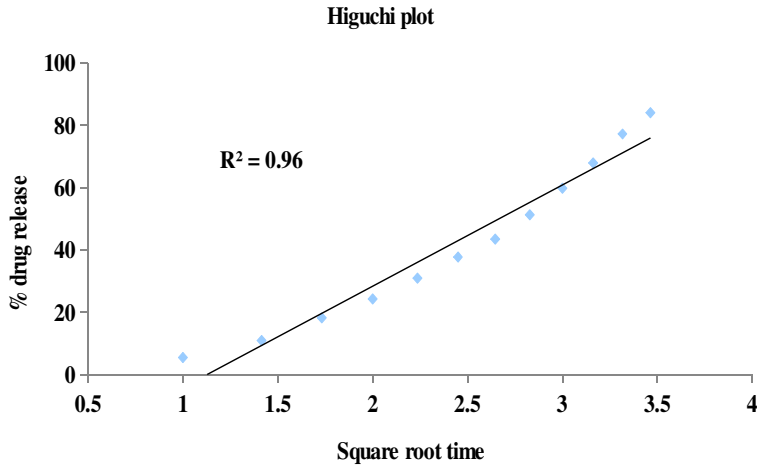


Fig 76: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F8)

Fig 77: Zero order Kinetic Plots of Formulation

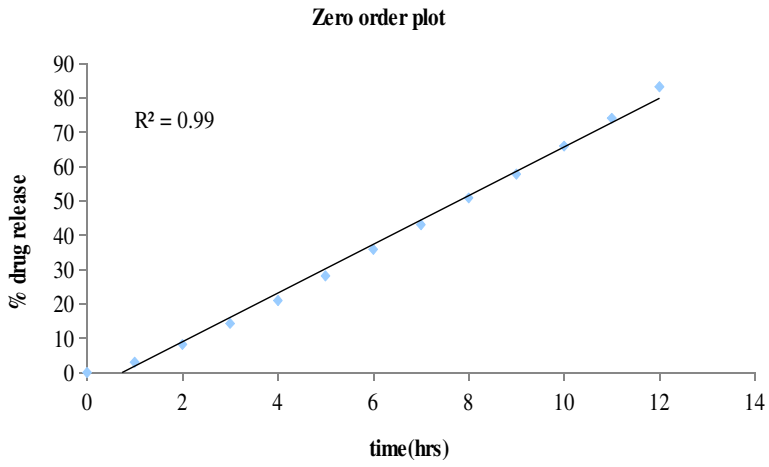


Fig 78: First order Kinetic Plots of Formulation

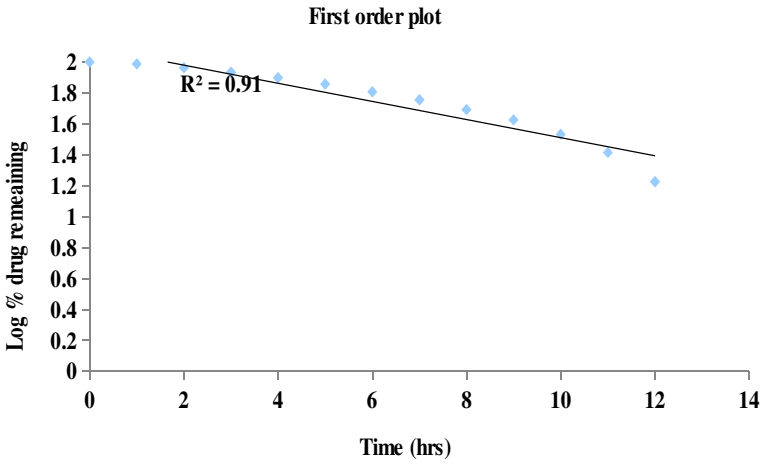


Fig 79: Korsmeyer Kinetic Plots of Formulation

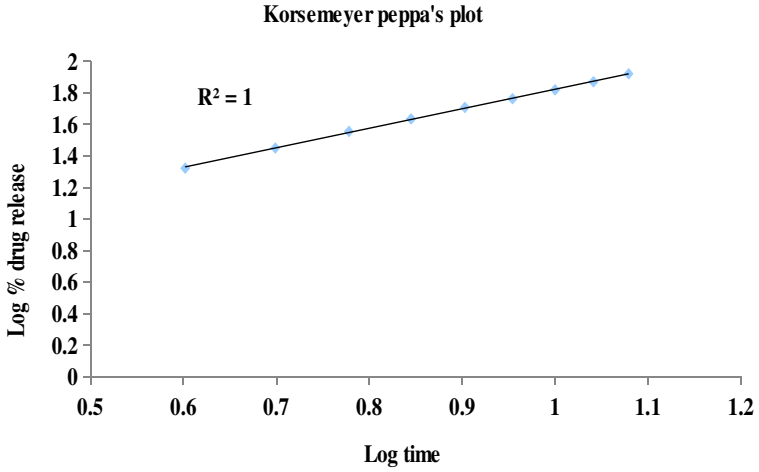
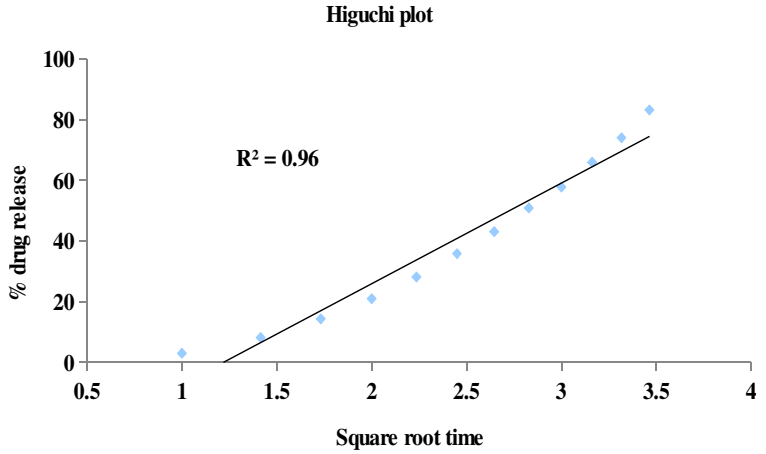


Fig 80: Higuichi's Kinetic Plots of Formulation



Ex vivo release Profile and Kinetic Plots of Formulation (F9)

Fig 81: Zero order Kinetic Plots of Formulation

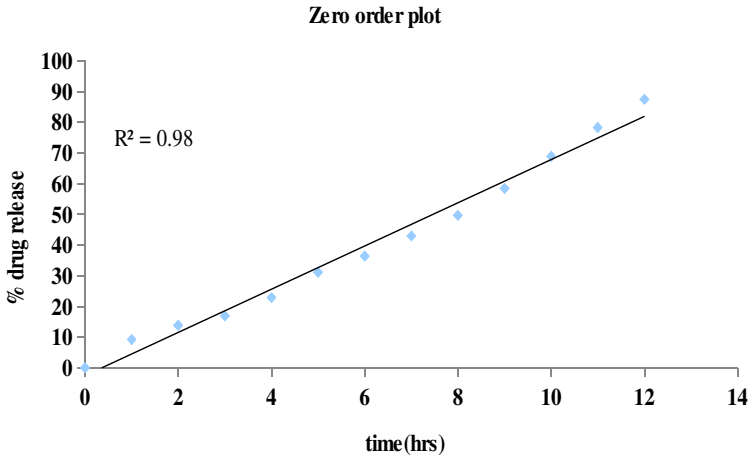


Fig 82: First order Kinetic Plots of Formulation

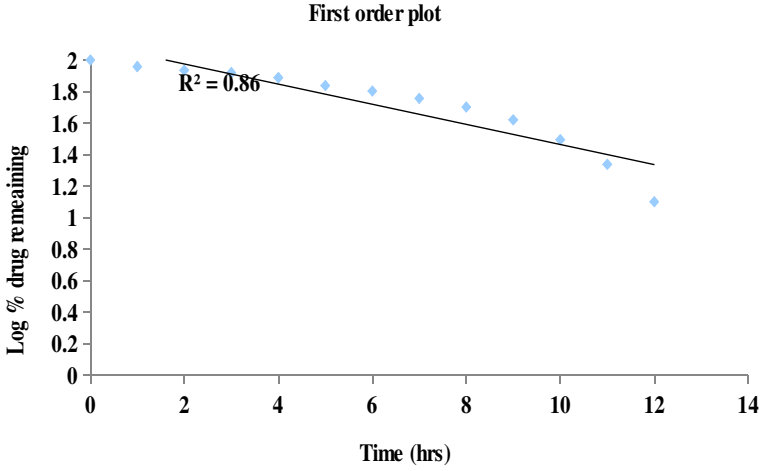


Fig 83: Korsmeyer Kinetic Plots of Formulation

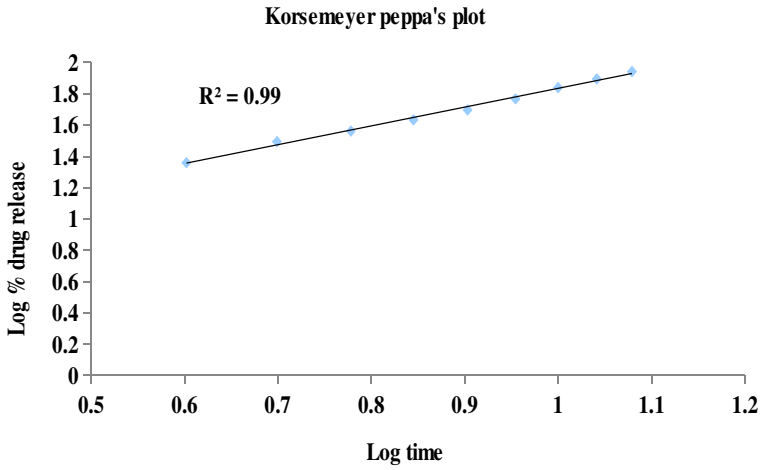
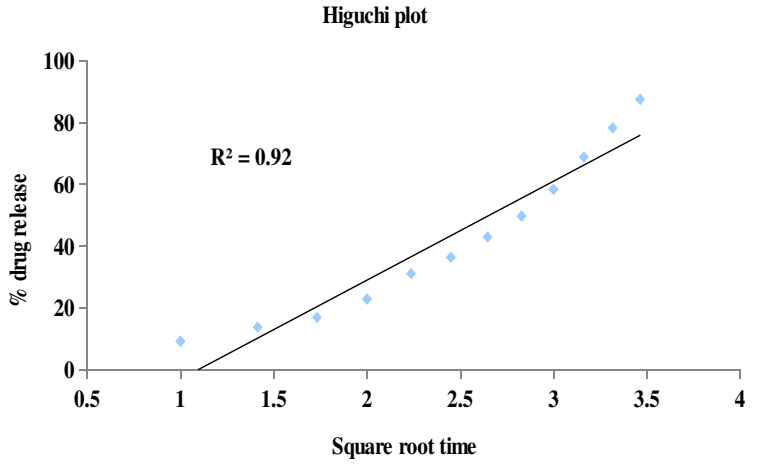


Fig 84: Higuichi's Kinetic Plots of Formulation



Discussion

9. DISCUSSION

In the present work efforts have been made to develop mucoadhesive properties of buccal tablet using direct compression technique involving mucoadhesive polymers like carbopol 934P, various cellulose ethers such as Hydroxy propyl methyl cellulose, Hydroxy ethyl cellulose and Polyvinylpyrolidone having different degree of solubility and swellability. Lactose was included as diluent. Ethyl cellulose was selected as a backing material because this hydrophobic polymer has very low water permeability thus providing an impermeable backing layer that prevents drug loss.

FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and polymers.

The blend of ingredients was analyzed for their physical characteristics. The angle of repose of formulation blends F1 to F9 were in the range of 31^0 45' ±0.1210 to 34^0 02' ±0.4347. The bulk density, tapped density, Compressibility index and Hauser' ratio were found in 0.316±0.0010 to 0.434± 0.0015 (gms/cc), 0.506±0.506 to 0.425±0.0066 (gms/cc), 19.280±1.201 to 13.760±1.021 and 1.238 ± 1.018 to 1.159± 0.013 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rate.

All the formulations pass the test for weight variation as per IP standard ± 7.5 % deviation.

Percentage of drug content for all formulations F1 to F9 were in the range of 99.01±0.56 to 96.95±0.20.

Thickness of F1-F9 formulations were found to be 3.49±0.005 to 3.21±0.010 mm. Hardness of all formulations F1-F9 were found to be 5.6 to 5.1 kg/cm^2. Percentage friability of all formulations F1-F9 were found to be 0.464 % to 0.0.361 %.

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets .High swelling index values of the formulations suggests that a large surface area is available for interaction. Swelling index was calculated with respect to time.

The surface pH of all the formulations were found to be within neutral pH with ±1. Low surface pH caused damage to contacting mucosal surface, if any surface pH changes occurred. Buccal tablets of all the formulations surface pH values in the range of 7.1 to 6.5 were within the acceptable limit. That indicates no risk of buccal damage or irritation in buccal cavity.

Mucoadhesion of buccal compact increases significantly with increase in carpobol concentration in the buccal layer. Increasing the concentration of carbopol 934 induced a moderate adhesion stronger than increasing concentration of HPMC, HEC and PVP. Increasing carbopol concentration follows this order BATCH I > BATCH II > BATCH III respectively. The almost same mucoadhesion profile were seen with in all batch of these formulations.

The drug release was affected by the concentration of HPMC K100M, Hydroxy ethyl cellulose, PVP. The concentration of carbopol 934P also controls the drug release. Carbopol 934P is a more hydrophilic polymer, it can swell rapidly. Therefore, decreasing of carbopol content delays the drug release. Although, HPMC K100M, Hydroxy ethyl cellulose and PVP has low bioadhesive properties, it was responsible to provide atorvastatin calcium drug release approaching zero order kinetics from the dissolution profile obtained and it was evident that the drug release rate was controlled.

Finally, the drug permeation profiles were investigated for all the buccal tablets. The ex vivo permeation studies showed that the released drug permeates the buccal membrane linearly.

Conculsions

10. CONCLUSION

The bright light development and evaluation of directly compressed mucoadhesive buccal formulations of atorvastatin calcium showed excellent bioadhesive properties with controlled release. The result of this study reveals that increasing the total polymer content of tablets leads to decrease in the rate of release. By adjusting the polymer grades and concentration it would be possible to control the release pattern with providing excellent bioadhesion at the same time. The development of mucoadhesive buccal tablets of atorvastatin calcium is one of the alternative route of administration to avoid first pass effect and provide controlled release .In future the in-vivo studies can be recommended for the directly compressed atorvastatin calcium mucoadhesive buccal tablets.

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